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Frequency of stavudine substitution due to toxicity in children receiving antiretroviral treatment in sub-Saharan Africa

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Introduction: Stavudine is a commonly used drug in paediatric antiretroviral treatment (ART) regimens. Due to toxicity concerns, however, the drug abacavir has replaced stavudine in first-line paediatric regimens in many countries. We describe the frequency of stavudine toxicity in children receiving ART at a treatment clinic in Soweto, South Africa.

Methods: Data on patient characteristics and outcomes of ART were collected from a cohort of 2222 HIV-infected children initiating ART between 2004 and 2008 when stavudine-containing regimens were routinely recommended. At several time-points after treatment initiation, we estimate the proportion of children where an attending clinician discontinued stavudine due to lipodystrophy, pancreatitis, lactic acidosis or peripheral neuropathy. Factors associated with stavudine-related toxicities were identified.

Results: At ART initiation, most children had advanced disease. The majority initiated an efavirenz/lamivudine/stavudine regimen ($n = 1422$), and 76% of children remained on their initial ART regimen after a median 19.9 months of ART. Replacement of stavudine due to drug toxicity occurred at a rate of 28.8 per 1000 child years on treatment (95% confidence interval = 23.6–35.2). Rates of toxicity increased with treatment duration (in their first year of ART stavudine was replaced in 0.5% of children, but after 3 years stavudine had been changed to abacavir in 12.6% of children). Toxicity was more common in older children and in girls. Lipodystrophy accounted for 87 of 96 toxic events.

Conclusion: Stavudine-associated toxicity resulting in single-drug substitution was uncommon in this cohort, though its frequency increased steadily with ART duration, especially with lipodystrophy. Where drug options are limited, stavudine remains a relatively well tolerated and effective option for children.

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Introduction

South Africa has one of the world's highest burdens of paediatric HIV [1], with HIV causing at least a third of the deaths of children under five [2]. Long-term antiretroviral therapy (ART) for HIV-infected children remains a major priority in the country. Stavudine formed part of the nucleoside reverse transcriptase inhibitor (NRTI) backbone of first-line ART regimens in South Africa in the initial ART guidelines in 2004 [3]. In 2010, however, following concerns about the drug's safety profile and guided by WHO recommendations [4], stavudine was removed from recommended first-line ART regimens in South Africa [5].

In adults, stavudine toxicity includes peripheral neuropathy, lactic acidosis, lipodystrophy and pancreatitis [6–11]. Although some of these toxicities are life-threatening, others can cause disability and disfigurement that impact on patient adherence and quality of life, and consequently on virological and clinical outcomes of ART. Although children may develop similar stavudine toxicities to adults, serious conditions appear less frequent [12–14]. Clinically significant lactic acidosis is uncommon in children receiving stavudine [12,15–17], although sub-clinical hyperlactataemia may occur in one-third of these children [15]. The most common stavudine-associated side effect in paediatric populations, lipodystrophic changes, affect between 5 and 33% of children, after 2–4 years of treatment [12,14,18,19]. NRTI-associated pancreatitis and peripheral neuropathy are rare in children [13,20–23]. Overall, however, there are few reports describing the frequency and characteristics of stavudine toxicity in paediatric populations in Africa.

This study describes the rate of stavudine-related toxicities requiring replacement of the drug with another in a paediatric population at a large tertiary hospital. Types of toxicities were also identified and risk factors for toxicity.

Methods

This retrospective cohort study was undertaken at Harriet Shezi Children's Clinic (HSCC), located at the Chris Hani Baragwanath Hospital in Soweto, Johannesburg, South Africa. HSCC is a public-sector outpatient facility providing medical and psychosocial care to HIV-infected children and is partially grant subsidized. We present data from ART-naive children who initiated a stavudine-containing ART regimen at HSCC between April 2004 and March 2008.

Patients and setting

First-line ART regimens used were consistent with national recommendations; stavudine, lamivudine and lopinavir/ritonavir (LPV/r) for children under 3 years, or stavudine, lamivudine and efavirenz for those initiating therapy when over 3 years of age and weight above 10 kg [3].

Prior to ART initiation, children were staged according to the WHO clinical staging, screened for tuberculosis and had baseline measures of CD4 count and percentage, full blood count and alanine aminotransferase. At each visit after ART initiation, patient information documenting medical history and clinical findings was recorded and entered into a Microsoft Access database. CD4 count and percentage, and plasma viral load were monitored 6 monthly to assess treatment response.

Children remained on the initial ART regimen provided they were: clinically well; undergoing immune recovery (increasing CD4 count and/or percentage); virally suppressed (plasma viral load < 400 copies/ml) and free of serious drug toxicities. Failing any of these criteria, a clinical decision was made to substitute a drug, change the entire regimen or temporarily cease ART. Abacavir was available to replace stavudine where required.

Definition of toxicities

Stavudine substitution due to toxicity was defined by clinical diagnosis of a stavudine-related toxicity (with or without supportive laboratory evidence) that resulted in the attending clinician replacing the drug with another (or temporary cessation of ART). Definitions of toxicities were based on the South African ART guidelines [3]. Specifically, HIV-associated lipodystrophy was clinically defined as: 'fat loss and/or fat accumulation in distinct regions of the body: increased fat around abdomen, buffalo hump, breast hypertrophy, and fat loss from limbs, buttocks and face' [3].

Data collection

This analysis draws on data in the patient electronic database and from a review of the individual patient files of those who developed stavudine-related toxicity or who died. Baseline variables, measured at ART initiation, included age at initiation, weight and height z-scores, initial ART regimen, CD4 percentage and plasma viral load (most recent CD4 percentage and viral load measures, less than 6 months before ART initiation).

Each child had a date of initiating ART, and a date of study outcome or censoring. Those remaining on stavudine and in active care were censored at their last clinic visit before 31 March 2008. Children who died, were referred elsewhere for care or were lost-to-follow-up (1 month overdue for their last clinic appointment) while still taking stavudine, were censored at last clinic visit. Patients who stopped stavudine due to virological failure or other nontoxicity-related factors were censored at date of drug discontinuation. Approval for the study was obtained from the Human Research Ethics

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Committee of the University of the Witwatersrand, South Africa.

Statistical methods

Analysis was conducted with Intercooled Stata 11.0 (Stata Corporation, College Station, Texas, USA) beginning with assessing possible univariable associations between stavudine substitution and sex, age at treatment initiation, ART regimen, and pre-ART anthropometry and baseline CD4 percentage. All variables were categorized and log-rank tests for equality of survivor functions were used to detect differences between rates of stavudine substitution in variable categories.

Multivariable models were constructed to investigate factors associated with the primary outcome, substitution of stavudine due to drug toxicity, as defined above. Variables associated with the outcome in univariable analysis or in similar previous studies were included in an initial multivariable model and retained if their removal markedly altered the model fit (backward fitting). A Cox Proportional Hazards model was constructed and the proportional hazards assumption was assessed using Schoenfeld residuals. Breslow's approximation method was used for tied failure times.

Results

Characteristics of participants at antiretroviral therapy initiation

Over the 4-year period, 2222 children initiated a stavudine-containing ART regimen (one child began a nonstavudine-containing regimen and has been excluded from this analysis). Median age at initiation was 4.7 years (inter-quartile range = 1.8–7.7). Two-thirds started lamivudine, stavudine and efavirenz ($n = 1422$). At treatment onset, 72% of children had WHO Stage 3 or 4 disease. Mean CD4 percentage was 12.7%, with more than two-thirds having a CD4 percentage below 15%. Most were wasted and stunted, and 27% ($n = 594$) were receiving treatment for tuberculosis.

Cohort description

Of the initial 2222 children, 82% ($n = 1831$) remained in active care at the clinic, with 76% ($n = 1690$) continuing a stavudine-containing regimen. Four percent ($n = 96$) stopped stavudine due to toxicity, 2% ($n = 45$) discontinued stavudine due to virological failure, 6% ($n = 138$) were referred elsewhere for continuation of ART, 6% ($n = 139$) lost-to-follow-up and 5% ($n = 114$) died. No deaths could be attributed to stavudine toxicity, although detailed information on cause of death was often unavailable.

The median duration of ART was 17.5 months. As children initiated ART at HSCC throughout the 4-year period, the cohort size increased over each calendar year. At the end of the study period, almost two-thirds ($n = 1403$) of the cohort had received ART for more than 1 year, 777 of these for more than 2 years, but only 10% ($n = 228$) had 3 or more years follow-up.

Stavudine toxicity

Ninety-six cases of stavudine toxicity occurred that resulted in its substitution with another drug at a rate of 28.8 per 1000 person-years of treatment [95% confidence interval (CI) = 23.6–35.2]. Most toxic events were lipodystrophy (87), with three cases of lactic acidosis, and two each of pancreatitis and peripheral neuropathy (two toxicities were undefined). Risk of toxicity requiring drug substitution increased with treatment duration, with 90% ($n = 85$) of toxicities occurring after 1 year of ART. Only 0.5% of children required substitution of stavudine in their first year of ART compared with 12.6% by 3 years. No association was detected between rate of stavudine replacement and clinical characteristics at time of ART initiation (WHO stage, tuberculosis status and weight for example; Table 1). Rates of drug substitution did decrease with each increase in immunological category, but a test for trend was not significant.

The final Cox model included sex and age. Rate of stavudine substitution with another drug due to toxicity was 1.5 times higher in girls than boys [95% CI adjusted hazard ratio (AHR) = 1.01–2.26]. Compared with other age groups, children 3–6 years at treatment initiation had the highest substitution rates (36.9 per 1000 person-years of stavudine), compared with 8.9 per 1000 person-years in children below 18 months when starting treatment (AHR = 3.71; 95% CI = 1.45–9.50; Fig. 1). Rate of toxicity in children receiving lamivudine/stavudine/efavirenz was 32.6 (95% CI = 26.0–40.9) per 1000 person-years compared with 17.6 (95% CI = 11.1–27.9) in children taking lamivudine/stavudine/LPV/r. Drug regimen was strongly dependent on age group however, and drug regimen could not be included in multivariate modelling. As age was strongly associated with toxicity and older children received lamivudine/stavudine/efavirenz, the association between drug regimen and toxicity might be due to confounding by age. However, children aged 2–4 years received either of these regimens. We thus examined the rate of toxicity in this age group. No difference was noted in toxicity rates in 2–4 years olds given lamivudine/stavudine/efavirenz (40.8/1000 person years on treatment; 95% CI = 24.6–67.6) versus lamivudine/stavudine/LPV/r (35.3/1000 person years; 95% CI = 19.0–65.7; $P = 0.67$), suggesting that age rather than drug regimen was the predominant predictor of toxicity.

Discussion

In this cohort in sub-Saharan Africa, drug changes as a result of stavudine toxicity were uncommon (28.8/1000

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Table 1. Clinical and laboratory characteristics of a cohort of 2222 children receiving antiretroviral treatment at Harriet Shezi Children's Clinic between 2004 and 2008 and rates of stavudine replacement by subgroup.

Characteristic at initiation of ART (n = total number included in analysis)	Number where stavudine replaced	Rate of stavudine replacement per 1000 person years of ART (95% CI)	*P-value*
Sex			
Female (n = 1020)	53 (5.2%)	33.6 (25.7–44.0)	
Male (n = 1102)	43 (3.9%)	24.5 (18.2–33.1)	0.07
Age at initiation of ART			
<18 months (n = 437)	5 (1.1%)	8.9 (3.7–21.3)	
18 months to 3 years (n = 323)	16 (5.0%)	30.4 (18.7–49.7)	
3–6 years (n = 528)	34 (6.4%)	36.9 (26.4–51.6)	
6–10 years (n = 588)	33 (5.6%)	34.3 (24.4–48.2)	
≥10 years (n = 249)	8 (3.2%)	22.3 (11.1–44.6)	0.06
Pre-ART WHO clinical stage			
Stage 1 or 2 (n = 567)	45 (7.9%)	36.6 (27.3–49.0)	
Stage 3 or 4 (n = 1359)	40 (2.9%)	23.5 (17.2–32.0)	0.92
Pre-ART CD4 cell percentage			
<15% (n = 1378)	77 (5.6%)	31.2 (25.0–39.0)	
15–24% (n = 455)	13 (2.9%)	21.5 (12.5–37.1)	
≥25% (n = 116)	2 (1.7%)	14.5 (3.6–58.2)	0.77
Initial ART regimen			
Stavudine/lamivudine/efavirenz (n = 1389)	75 (5.4%)	32.6 (26.0–40.9)	
Stavudine/lamivudine/LPV/r (n = 728)	18 (2.5%)	17.6 (11.1–27.9)	
Other (n = 9)	3 (33.3%)	314.9 (101.6–976.4)	<0.001*
Weight z scores			
<−3 (n = 573)	21 (3.7%)	24.2 (15.8–37.2)	
−3 to −2 (n = 439)	23 (5.2%)	33.0 (22.0–49.7)	
−2 to −1 (n = 535)	27 (5.0%)	30.7 (21.0–44.7)	
≥−1 (n = 463)	23 (5.0%)	31.7 (21.0–47.6)	0.70
Height z scores			
<−3 (n = 735)	42 (5.7%)	35.3 (26.1–47.7)	
−3 to −2 (n = 572)	20 (3.5%)	21.8 (14.1–33.8)	
−2 to −1 (n = 441)	20 (4.5%)	30.0 (19.3–46.4)	
≥−1 (n = 246)	11 (4.5%)	29.6 (16.4–53.4)	0.43
TB treatment at time of ART initiation			
Yes (n = 568)	21 (3.7%)	26.2 (17.1–40.2)	
No (n = 1558)	75 (4.8%)	29.6 (23.6–37.2)	0.92

All P values are log-rank test. ART, antiretroviral treatment; TB, tuberculosis; WHO, World Health Organisation.
*P value here excludes the other category.

child-years of treatment), and especially rare in children under 18 months. Only 4.3% of all children on a stavudine-containing regimen changed drugs because of toxicity, lower than in other cohorts [12,14,18,19,24]. Consistent with previous literature, the predominant toxicity was lipodystrophy and toxicity clearly rose with duration of drug exposure. It is, however, difficult to directly compare rates of toxicities between studies as there is considerable variation in study populations and definitions of toxicity. We propose that criteria used to identify toxicities caused by antiretroviral drugs be standardized to ensure consistency of diagnosis across treatment sites.

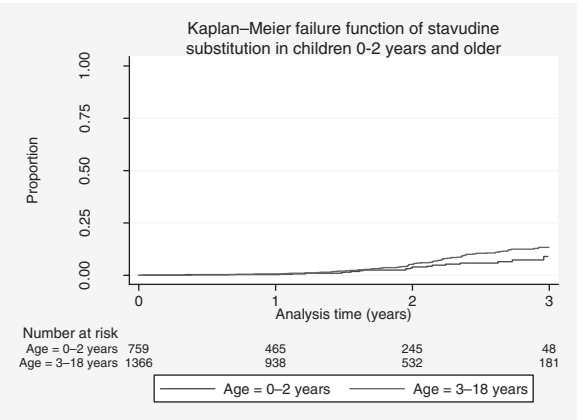


Fig. 1. Cumulative rates of stavudine toxicity over time in children less than and greater than 3 years of age at the time of treatment initiation.

The retrospective nature of the study design limits our analysis, as does the reliance on a clinical diagnosis of lipodystrophy, which may be subjective. Also, potentially undiagnosed cases of toxicity in the lost-to-follow-up and demised groups means that the toxicity rates may have been higher. Finally, the finding that toxicity was more frequent in girls than boys might stem from increased vigilance and clinical attention paid to girls receiving stavudine, as clinicians were aware that these toxicities are substantially more common among adult women than men.

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Stavudine has been replaced with abacavir in first-line ART regimens in South Africa, however, children already receiving stavudine will continue this drug and its use remains widespread, particularly in Africa. More detailed investigation is required of the long-term effects of stavudine-related dyslipidaemias, and consequent cardiovascular and metabolic outcomes. These could be assessed in a national register, or a series of sentinel sites, which monitor important short-run and long-run toxicities. Overall, however, this study suggests that stavudine is an effective and well tolerated antiretroviral agent for paediatric use, especially in the short term, and should remain within the options considered for treatment regimens.

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Conflicts of interest

There are no conflicts of interest.

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