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Frequency of stavudine substitution due to toxicity in children receiving antiretroviral treatment in Soweto, South Africa

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Frequency of stavudine substitution due to toxicity in children receiving antiretroviral treatment in Soweto, South Africa

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    a. Ethics clearance
    b. Copy of published article

Declaration by author

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work.

Signed by Megan Palmer _____

Date _____

Declaration by co-authors

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The co-author's declaration applies to the following manuscript
Frequency of stavudine substitution due to toxicity in children receiving antiretroviral treatment in Soweto, South Africa

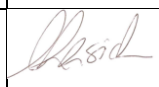
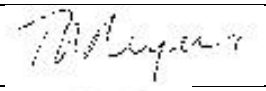
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1	Formulation of the concept phase of the study – including literature review, definition of study aim, protocol submission, planning of data collection strategies	C
2	Collection and collation of data for the study / article	C
3	Interpretation of results	C
4	Writing of the journal article	C

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Title page

Frequency of stavudine substitution due to toxicity in children receiving antiretroviral treatment in Soweto, South Africa

Megan Palmer

Abstract

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-positive 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 three years stavudine had been changed to abacavir in 12.6% of children). Toxicity was commoner in older children and in girls. Lipodystrophy accounted for 87 of 96 toxic events.

Conclusions

Stavudine-associated toxicity resulting in single-drug substitution was uncommon in this cohort, though its frequency increased steadily with ART duration, especially with lipodystrophy. Lipodystrophy was significantly more common in this paediatric cohort than any other stavudine-associated toxicity – a pattern that is dissimilar than that seen in data from adult populations. Where drug options are limited, stavudine remains a relatively safe and effective option for children.

Introduction

South Africa (SA) remains at the epicentre of the HIV pandemic. UNAIDS estimates that 5.6 million South Africans are HIV-positive.(1) This makes the number of HIV-positive people in SA higher than in any other country in the world. SA Department of Health statistics indicate that 29.5% of pregnant women attending public antenatal clinics are HIV positive (2) placing the paediatric population at high risk due to vertical transmission.

Despite improvements in the national PMTCT program the HIV prevalence rate in the South African paediatric population remains high. UNAIDS estimates from 2011 are that 460 000 (410 000 - 520 000) children in this country are HIV-positive (1), and Statistics South Africa reports that 377 097 children in South Africa are in need of antiretroviral therapy (ART).(3) Worldwide, South Africa is one of only 12 countries that have failed to decrease under-five mortality rate since 1990, and at least 35% of deaths in this age group are attributed to HIV (4). Providing access and long-term ART to HIV-positive children remains a priority in this country.

In April 2004 the SA government launched its Comprehensive Care and Management Treatment Plan (CCMTP) which provided access to ART for all children requiring it as outlined in the SA National Guidelines.(5) These guidelines were based on the first World Health Organisation (WHO) guidelines which were published in 2003.(6)

Stavudine forms an integral part of first line ART regimens in both adults and children in many low- and middle-income countries as it is cheap, easily accessible, effective, requires less routine laboratory monitoring than some other NRTIs (for example AZT), and is available in fixed-dose combinations as well as both capsule and syrup formulations.

Between 2004 and 2010, in accordance with the initial SA National Guidelines, stavudine together with lamivudine formed the nucleoside reverse transcriptase inhibitor (NRTI) backbone in first-line ART. These two drugs were most commonly combined with lopinavir/ritonavir in children under three years of age, and efavirenz in children older than three years of age.

Over the years evidence has emerged, largely from data from adult cohorts, concerning stavudine's side effect profile. The NRTIs cause clinical toxicities on the basis of their ability to inhibit the mitochondrial DNA polymerase gamma enzyme. DNA polymerase gamma catalyses the formation of new DNA strands and is integrally involved in DNA synthesis. Inhibition of this enzyme interferes with mitochondrial replication and function. Mitochondria contain the enzymes and proteins necessary for the generation of ATP, and thus mitochondrial toxicity results in failure of ATP production and inhibition of oxidative phosphorylation. This can affect virtually all organ systems in the body, particularly those with a high energy demand.(7, 8)

In adults, the NRTIs can cause a range of side effects on the basis of mitochondrial toxicity including peripheral neuropathy, lactic acidosis, lipodystrophy and pancreatitis.(9-13) While some of these toxicities (such as lactic acidosis) are life-threatening, others (such as lipodystrophy) can cause disability and disfigurement that impact on patient adherence and thus virological and clinical success of ART.

Local data from adult populations on stavudine-containing regimens report high rates of toxicities, confirming what has been found internationally.(10, 14) Stavudine-related toxicities requiring drug substitution occurred at a rate of 21% after 3 years on treatment in a Cape Town population.(15) Wong et al reported that 44.1% of adult patients receiving a stavudine-containing regimen at Charlotte Maxeke Hospital developed a treatment related side effect, with 19.7% of these severe enough to require a regimen change.(16) High rates of symptomatic hyperlactataemia and lactic acidosis, with high associated mortality, amongst adult women on stavudine-containing regimens have been published from Chris Hani Baragwanath Hospital.(17)

Rates of stavudine toxicity in general seem to be increased with longer duration on ART – of significance in the South African context as more people are starting ART and remaining on the drugs for longer. Other factors increasing stavudine toxicity rates are the combination of stavudine with didanosine, using higher dose stavudine and being pregnant while on the drug. More specifically rates of stavudine associated lactic acidosis appear to be higher in women with high body mass indices (BMIs).(14, 17)

While children may develop similar stavudine toxicity to adults, the available literature suggests that serious toxicities occur less frequently in children (18-20). Although sub-clinical hyperlactataemia has been reported to occur in approximately one third of children on ART regimens that include an NRTI (21, 22), its clinical significance is uncertain and the overall prevalence of clinically-significant lactic acidosis is low (18, 22-24).

The incidence of NRTI-associated pancreatitis in children was reportedly as high as 17% in the 1990s (25), but more recent studies indicate that elevated amylase/lipase with clinical pancreatitis occurs in fewer than one percent of children (26, 27). It is seen more frequently in ART regimens containing stavudine and didanosine (or the combination thereof) than with other NRTIs.(27)

Peripheral neuropathy is also reportedly less frequent in children than in adults (20) with a low incidence rate of 0.23 per 100 person-years reported from a large cohort of children in the United States.(19)

Lipodystrophic changes have been reported in 5% to 33% of children who have been on ART for between 2 and 4 years, and are the most common stavudine-associated side effect in paediatric populations (18, 28-30). The term lipodystrophy refers to a change in body fat distribution and encompasses lipoatrophy, lipohypertrophy and a combination thereof. Lipoatrophy is characterised by a loss of subcutaneous fat, particularly from limbs, buttocks and temporal regions and is the commonest fat redistribution pattern associated with stavudine. Lipohypertrophy refers to the accumulation of fat tissue both subcutaneously

and viscerally – subcutaneous fat is usually deposited truncally and dorsocervically, giving patients a Cushingoid appearance. A combination occurs when fat is redistributed so that limbs, buttocks and face appear wasted, but truncal and dorsocervical fat is increased. Although lipohypertrophy or a combination of atrophy and hypertrophy are noted in patients on long-term ART, they are less typically associated specifically with stavudine toxicity. Suggested risk factors for the development of lipodystrophy include age, length of time on ART, choice of ART (PI and/or NRTI-containing regimens) and a low CD4 count at the start of therapy.(29, 31)

The studies reporting stavudine toxicity have been small, most commonly from European populations and there are few studies describing stavudine toxicity in paediatric populations in Africa. This is important as occurrence of toxicities can vary considerably between population groups.

As the ART programme in SA matures, focus has shifted from not only initiating ART for a large number of children, to maintaining children on ART and addressing the long-term side effects of drugs - some of which may impact on adherence. Due to the cumulative evidence over the years regarding stavudine's side effect profile the WHO – largely guided by data obtained from adult populations - now recommends that stavudine should be avoided in first-line ART regimens (32).

In 2010, in accordance with these recommendations updated South African guidelines were published – stavudine was replaced with abacavir (ABC) or tenofovir (TDF) for paediatric and adult ART regimens respectively (33). TDF and ABC have replaced stavudine in first-line ART regimens in most high-income countries, however these drugs pose significant cost challenges in resource-constrained settings, with stavudine about one quarter the price of TDF at the time of the guideline changes.

Although stavudine is no longer prescribed in first-line regimens in South Africa, children who started the drug in accordance with guidelines prior to 2010 who are virally suppressed and free of side effects will remain on the drug. Stavudine remains part of first line regimens in many other resource-limited countries – a survey in March 2006 of 23 resource-limited countries indicated that 70% of adults were on stavudine as part of their first-line ART regimen.

This study aimed to describe the rate of stavudine-related toxicities requiring drug substitution in a paediatric population receiving ART at a large tertiary hospital in Soweto, South Africa. Additionally, we identified types of toxicities and the baseline characteristics associated with these toxicities.

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 partially grant subsidized. The clinic, now the largest paediatric HIV clinic in the country, began in 1997 with the aim of providing comprehensive medical and psychosocial care to HIV-positive children. Children accessing care at HSCC are referred to the clinic predominantly from the CHBH's inpatient paediatric wards and outpatient paediatric department, but also from surrounding clinics, hospitals and private practitioners

When the South African Department of Health launched its Comprehensive Care and Management Treatment Plan for HIV (5) in 2004, the clinic was able to offer triple antiretroviral therapy for all children eligible for ART based on national guidelines. Here we present data from all children who initiated a stavudine-containing ART regimen at HSCC between April 2004 and March 2008.

Patients and setting

All services at HSCC are provided without user fees. The clinic is staffed by doctors and nurse clinicians with various levels of experience, and a paediatrician and training specialist are available for consultation. Throughout the study period, the first-line ART regimen consisted of stavudine, lamivudine, and lopinavir/ritonavir (Kaletra®) for children under 3 years, or

stavudine, lamivudine and efavirenz for those initiating therapy when over 3 years of age and weight above 10kg.

At the initial clinic visit, children were staged according to the WHO clinical staging and pre-treatment CD4 count and percentage, full blood count and alanine aminotransferase measured. As South Africa has a high burden of tuberculosis infection, children were assessed by clinicians for evidence of tuberculosis and investigated accordingly.

Consistent with standard of care at the clinic, children attended a visit two and then four weeks after ART initiation, and three monthly thereafter. At each visit, a doctor or nurse clinician documented clinical findings in patient files, and completed a standardised patient form, later entered into a Microsoft Access database. Electronic data were stored on a central electronic database, intended for real-time tracking of individual patients and for later cohort analysis. CD4 count and percentage, and plasma viral load were measured six monthly to assess immunological and virological response to treatment.

Children remained on the initial ART regimen provided they were: demonstrating no clinical symptoms suggestive of ART-associated toxicities; showing evidence of immune recovery (increasing CD4 count and/or percentage); virally suppressed (plasma viral load <400 copies/ml) and free of serious drug toxicities. Should any of these criteria not have been met, a clinical decision was made to change the entire ART regimen, substitute one drug for another or, in very rare instances, temporarily stop ART (for life-threatening toxicities to

allow the child to recover before introducing a new ART regimen). Abacavir was available for substitution for stavudine, where required.

Inclusion and Exclusion Criteria

All children receiving ART at HSCC were considered for this analysis.

Inclusion criteria

- between the ages of 2 weeks and 18 years
- initiated a stavudine-containing regimen during the time period 1 April 2004 and 31 March 2008
- had one subsequent clinic visit to the date of initation of ART. This visit must have taken place prior to 31 March 2008

Exclusion criteria

- children who initiated a stavudine-containing regimen elsewhere and who subsequently received care at HSCC, but who did not have a clear date for starting ART
- children starting ART with NRTI's other than stavudine

Definition of outcomes

- Each child included in this review had a date of initiating a stavudine-containing regimen and a date at which an outcome was identified.
- Possible outcomes (see figure 1)
  - Still attending HSCC and still on stavudine

- No longer on stavudine at HSCC because
    - Demised
    - Referred elsewhere for care, and still on stavudine at last HSCC visit
    - Defaulted follow up, whereabouts not known
    - Still at HSCC, but no longer on stavudine because
        - Developed stavudine related toxicity
        - Developed virological failure

Definition of toxicities

In this analysis, stavudine substitution due to toxicity was defined by clinical diagnosis (with or without supportive laboratory evidence) of a stavudine-related toxicity that required drug substitution (or temporary ART cessation). Case definitions within the South African guidelines were used to define toxicities (5).

HIV-associated lipodystrophy, in particular, was a clinical diagnosis, encompassing both lipoatrophy and lipohypertrophy and 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'. Although it is more accurate and specific to describe the fat redistribution pattern associated with stavudine toxicity as 'lipoatrophy', we have elected to use the broader term of 'lipodystrophy' as this is the term used in the National Guidelines on which our definitions of toxicites were based and it was still the widely used term in paediatric publications at the time that this study was undertaken.

Data collection

Data for the analysis were assembled from the electronic database. Where data were missing or implausible, individual patient files were reviewed. Baseline data, measured at ART initiation, included age at ART initiation, weight and height z-scores, initial ART regimen, CD4 percentage and plasma viral load (most recent CD4 percentage and viral load results within 6 months before ART initiation).

Each child had a date of initiating ART and a date of 'outcome'. Children who remained in active care and on a stavudine-containing regimen at the end of the study period, were censored at their last clinic visit before 31 March 2008. Those that demised, were referred elsewhere for care or were lost-to-follow-up while still taking stavudine, were censored at their last clinic visit. Definition of lost-to-follow-up was a child not having contact with the clinic staff four months before the end of the study period (namely, at least one month overdue for their last routine visit). Patients who stopped stavudine due to virological failure or other non-toxicity-related factors were censored at the date of drug discontinuation. For those whose outcome was stopping stavudine due to the development of a toxic event, further review of their individual clinic files was conducted to identify the specific type of toxicity. Individual files were also reviewed when the patient outcome was unclear from the database, and for all deaths to determine whether deaths could be attributed to stavudine-related toxicity.

Approval for the study was obtained from the Committee for Research on Human Subjects of the University of the Witwatersrand, Johannesburg, South Africa.

Statistical methods

Intercooled Stata 11.0 (Stata Corporation, College Station, Texas, USA) was used for statistical analysis. Descriptive analysis and summary statistics were performed as a first step. Possible univariable associations between stavudine substitution and gender, age at time of treatment initiation, ART regimen, and pre-ART anthropometry and baseline CD4 percentage were then investigated. All variables were categorised 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 study outcome. The primary outcome variable was 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 removal of the variable 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 time of ART initiation

Over the four year period, 2222 children initiated a stavudine-containing ART regimen at HSCC and were included in this analysis (figure 1). Median age at ART initiation was 4.7 years (IQR=1.8–7.7). Two thirds of children started an ART regimen comprising lamivudine, stavudine and efavirenz (n=1422).

At time of ART initiation, most children had advanced HIV disease, both clinically and immunologically. Seventy two percent of children had WHO Stage 3 or 4 disease, and mean CD4 percentage before starting ART was 12.7% with more than two thirds initiating ART with a CD4 percentage below 15%. Most were wasted and stunted, with mean weight-for-age z-score of -2.3. Half of the children were 2 or more standard deviations below weight for age and 65% fell 2 standard deviations below height for age. At ART initiation, 27% (n=594) of children were receiving treatment for tuberculosis.

Cohort retention

At the end of the study period 82% (n=1831) of the cohort were still receiving care at HSCC. Of the 2222 children that initiated ART during the study period 76% (n=1690) remained at the clinic on a stavudine-containing ART regimen, 4% (n=96) had stopped stavudine due a stavudine-related toxicity, 2% (n=45) had stopped stavudine due to virological failure, 6% (n=139) were lost-to-follow-up, 6% (n=138) were referred elsewhere for continuation of ART

and 5% (n=114) had died (figure 1). Although details regarding cause of death were sought for each patient who died while on stavudine, sufficient information was not available to identify whether any deaths were attributable to stavudine-related toxicity.

The median duration of ART was 17.5 months. As children initiated ART at HSCC throughout the four year period, the cohort size increased steadily in each calendar year. From the start of the government ART programme in 2004 until the end of 2005, 982 children had initiated stavudine-containing ART regimens; a further 1142 children started ART in 2006 and 2007, and 98 children were initiated between January and March 2008. At the end of the study period almost two thirds (n=1403) of the cohort had received ART for more than one year, 777 of these took ART for more than two years, but only 10% (n=228) had three or more years follow up.

Stavudine drug toxicity

Ninety six cases of stavudine toxicity resulting in substitution occurred, at a rate of 28.8 per 1000 person-years of treatment (95%CI=23.6-35.2). Risk of developing stavudine toxicity requiring drug substitution increased with time on treatment, with 90% (n=85) of toxicities occurring after one year of ART; only 0.5% of children required stavudine substitution in their first year of ART, 4.5% after two years stavudine and 12.6% by three years. Eighty seven of the toxic events were lipodystrophy, two were due to symptomatic hyperlactataemia, there was one case of lactic acidosis and two each of pancreatitis and peripheral neuropathy (two toxicities were undefined).

Factors associated with stavudine substitution

Clinical and laboratory characteristics at time of ART initiation were similar between the children who did and did not have a stavudine toxicity requiring substitution. No difference was detected between substitution rates in those with WHO Stage 1 and 2 disease, and those with WHO Stage 3 and 4 disease. Although rates of drug substitution decreased as immunological category increased, a test for trend was not significant. Also no association was detected between toxicity-related substitution, and weight and height z-scores at time of ART initiation, and tuberculosis co-morbidity.

The final Cox model included gender and age. The rate of stavudine substitution 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 aged 3 to 6 years at time of treatment initiation had the highest substitution rates (36.9 per 1000 person-years of stavudine), compared to 8.9/1000 person-years in children below 18 months when starting treatment (AHR=3.71; 95%CI=1.45-9.50). Rate of toxicity in children receiving lamivudine/stavudine/efavirenz was 32.6 (CI=26.0-40.9) per 1000 person-years compared with 17.6 (CI=11.1-27.9) in children taking lamivudine/stavudine/Kaletra®. However, regimen choice is determined by child age, thus in an attempt to evaluate whether differences in rates of toxicity-related stavudine substitution between these regimens were attributable to the regimen or to the child's age at treatment initiation, a subgroup analysis was performed in children aged two to four years. Toxicity rates in this age group were 40.8

(CI=24.6-67.6) per 1000 person years on treatment in those on lamivudine/stavudine/efavirenz and 35.3 (CI=19.0-65.7) in those on lamivudine/stavudine/Kaletra® (*P*=0.67) suggesting that age is the pre-dominant determinant of toxicity and confounding by age likely accounts for the different rates between the regimens.

Discussion

This analysis provides new insight into the rate of drug changes as a result of stavudine toxicity in a paediatric population attending a public sector facility in sub-Saharan Africa. Drug changes as a result of stavudine-associated toxicity occurred at a rate of 28.8 per 1000 child-years of treatment in our analysis, with 4.3% of all children on a stavudine-containing regimen changing drugs because of toxicity – this is lower than previously published cohorts (18, 28-30). Consistent with the other literature and strikingly dissimilar from adult data, the predominant toxicity in this paediatric cohort was lipodystrophy and toxicity clearly increased with duration of drug exposure. It is difficult to directly compare rates of toxicities between studies as studies populations differ markedly, previous reports did not primarily examine stavudine substitution due to toxicity and definitions of lipodystrophy varied across studies.

Amaya et al (28) described a prevalence of fat redistribution of 18% among 48 children in the United States; however this analysis excluded children with AIDS defining events (complicating comparison with our cohort of children with advanced HIV disease) and implicated the NRTIs as a group rather than stavudine particularly. Beregszaszi (29) and Jacquet (30) reported that a quarter to a third of children receiving ART had clinical lipodystrophy or associated dyslipidaemias in European cohorts. However, children in both these analyses were on several ART regimens, with the protease inhibitors also being implicated in dyslipidaemias, and an association between stavudine and lipodystrophy was not specifically described.

Median age in our cohort was 4.7 years. With evidence in the literature suggesting that older age may predispose to development of lipodystrophy, the fact that the Beregszaszi cohort had a median age of ten years, and that children under three years were excluded from Jaquet's analysis indicates that children in these cohorts were already at higher risk for developing stavudine toxicities by virtue of their older age. The age distribution of children in our cohort is similar to previous reports in sub-Saharan Africa (34).

The European Lipodystrophy Group published data from 477 children and found that 26% of them had at least one sign of fat redistribution. When controlling for other risk factors, being on a stavudine-containing regimen remained the strongest risk factor for developing lipodystrophy in this European cohort. Consistent with our findings, this group also found female gender and increasing age to be associated with lipodystrophy (35). The case definition of lipodystrophy is more sensitive than ours as it relies on the identification of just one physical sign rather than a constellation of signs. This might explain the lower prevalence of lipodystrophy in our cohort than previous findings. Our diagnosis of lipodystrophy, made by the attending clinician is more subjective and less sensitive compared with, for example, a combination of skin-fold thickness, body fat percentage and clinical phenotype as used in several other studies (29, 30).

Interestingly both the European Lipodystrophy Group and Beregszaszi suggested that lipodystrophy rates were lower in children of African descent; consequently findings from American and European cohorts may not be generalisable to the South African population. Reports from paediatric populations in African countries are limited but a study of non-

Caucasian Malawian children reported that only 11 of 1434 children on ART changed their first-line ART regimen due to stavudine-related toxicity and there were no reported cases of lipodystrophy (34).

The reason for the seemingly lower rates of stavudine-associated lipodystrophy reported from African settings when compared with data from European and American cohorts is unclear. Aside from potential genetic or environmental factors, the limited alternatives to stavudine in these resource constrained settings might discourage clinicians from changing or stopping therapy for toxicities which were not life-threatening. In our context, however there was access to both abacavir and zidovudine as alternatives to stavudine. Whether a 'Westernised' lifestyle and diet may be implicated as contributing to the development of lipodystrophy in the American and European cohorts is unknown; however eight of the nine children who developed lipodystrophy and completed a diet history in Amaya's American cohort were classified as having high fat diets. (28)

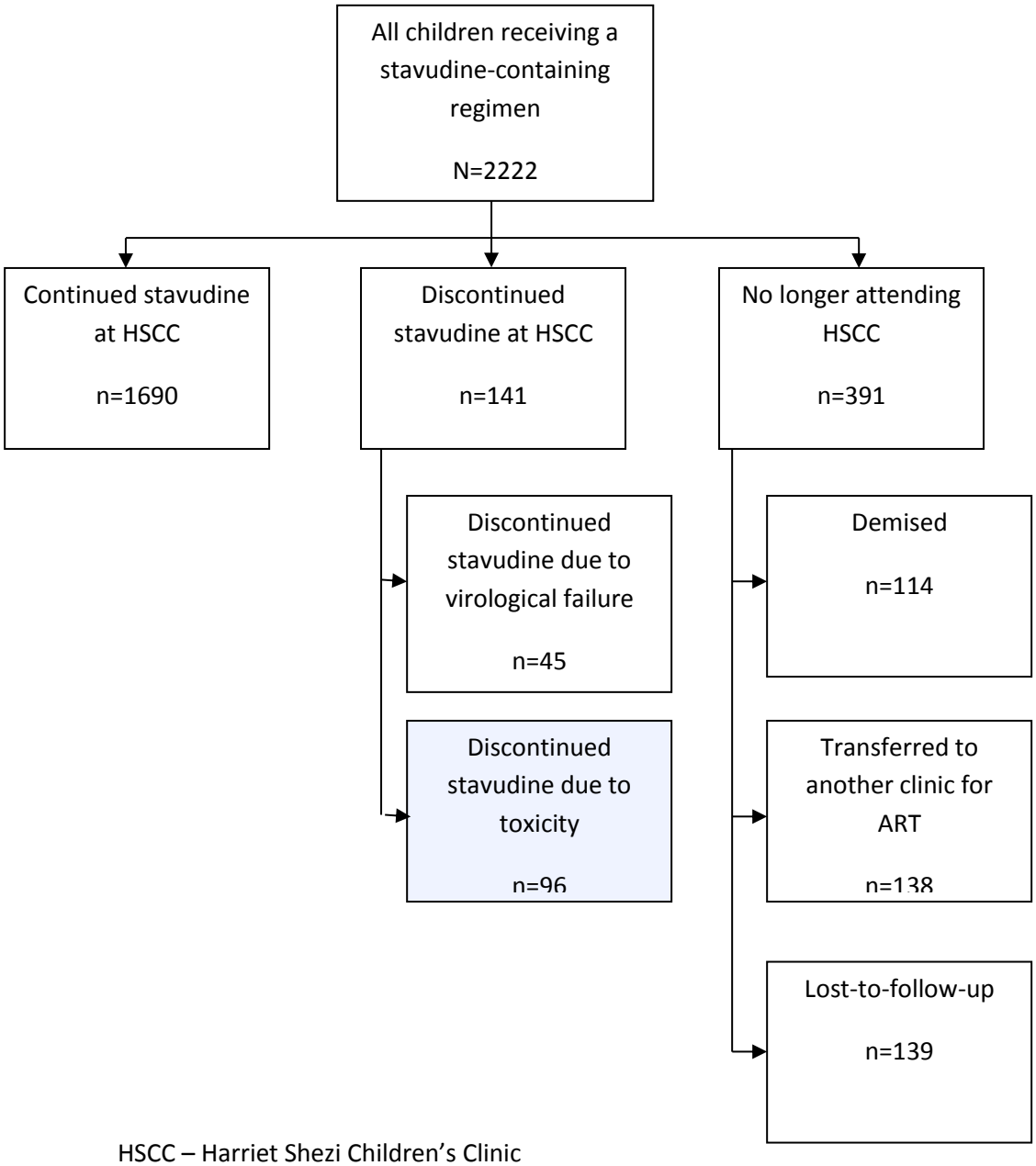
Limitations of our analysis are the retrospective nature of the study design, the reliance on a clinical diagnosis of toxicity which can be subjective, and the children lost-to-follow-up or who had died who may have had undiagnosed stavudine toxicity . It is likely that the children that were lost-to-follow-up represent a group where toxicity may have been higher than the rest of the cohort, as unwanted drug associated side-effects may have contributed to treatment default. Attempts were made to identify cause of death amongst the children who demised. This was, however, largely not possible due to the unavailability of clinical

information from around the time of death. Deaths caused by stavudine toxicity, especially out-of-hospital deaths, may have been missed.

Although stavudine has been removed from first-line ART regimens in South Africa, children who are already receiving the drug will continue on this therapy and its use remains widespread, particularly in resource-limited settings. Abacavir has already replaced stavudine in some countries and is largely accepted as a safer agent in paediatrics in terms of long-term tolerability, despite the risk of potentially fatal abacavir hypersensitivity reaction and high cost.

More detailed pharmacovigilance is required of the long-term effects of stavudine-related dyslipidaemias, and consequent cardiovascular and metabolic outcomes. These could be assessed in national registers, or a series of sentinel sites which monitor important short- and long-run toxicities. There is scope for future research regarding why lipodystrophy is consistently found as the overwhelmingly predominant toxicity in paediatric populations when compared with adults. Overall, however, this study suggests that stavudine is an effective and safe antiretroviral agent for paediatric use, especially in the short term, and should remain within the options considered for treatment regimens.

Figure 1 Outcomes of stavudine-containing antiretroviral treatment in Soweto South Africa

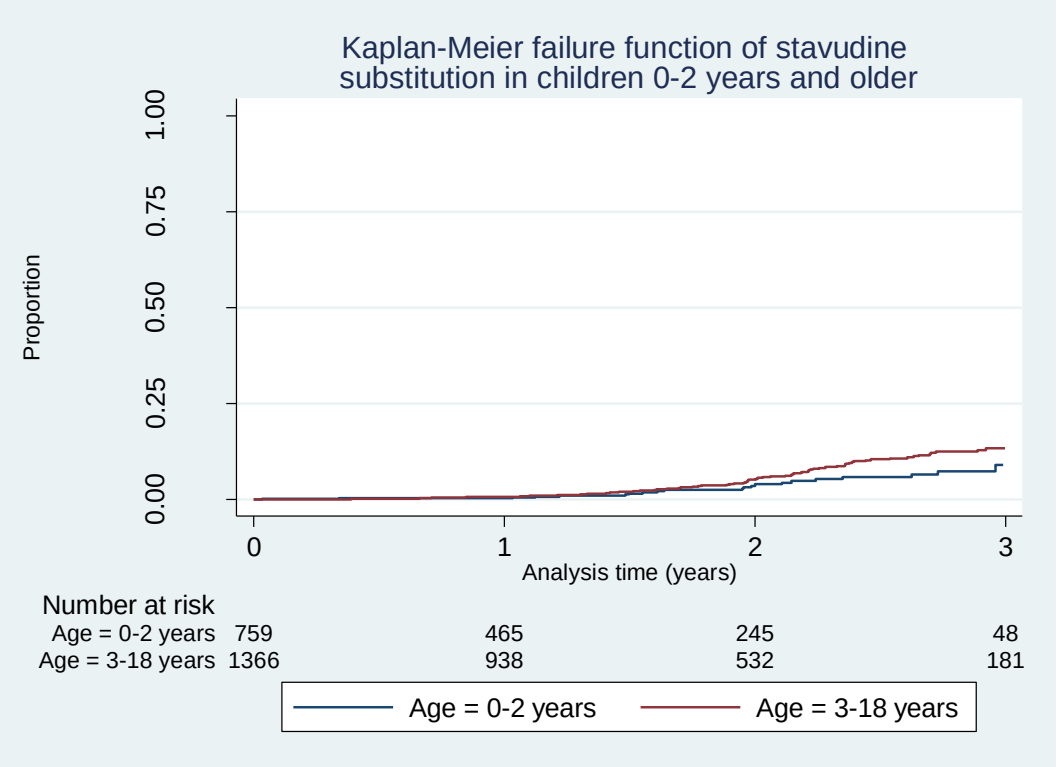


HSCC – Harriet Shezi Children's Clinic

ART – Antiretroviral Therapy

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

Figure 2 – Cumulative rates of stavudine toxicity over time in children less than and greater than three years of age at the time of treatment initiation.



Characteristic at initiation of ART (n=total number included in analysis)	Number with stavudine-substitution	**Rate of stavudine substitution** per 1000 person years of ART (95% CI)	***P-value***
Gender			
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-3years (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%)	36.65.9 (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/~~kaletra~~Kaletra (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. WHO – World Health Organisation. TB – tuberculosis. ^*P* value here excludes the other category

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Appendices

Ethics clearance certificate and copy of published article

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Megan Palmer

CLEARANCE CERTIFICATE	**M10642**
PROJECT	Rate of Toxicity-Related Substitution of Stavudine in a Cohort of Children Receiving antiretroviral Treatment at CH Baragwanath Hospital Soweto, aouth Africa
INVESTIGATORS	Dr Megan Palmer.
DEPARTMENT	Department of Paediatrics
DATE CONSIDERED	25/06/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 28/06/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr T Meyers

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...