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Full Length Research Paper

Comparative tolerability and efficacy of stavudine 30 mg versus stavudine 40 mg in patients on combination antiretroviral therapy in Kenya

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Stavudine- containing regimens are currently the most widely used first-line anti-HIV treatment option in Kenya. This study compared the efficacy and tolerability of stavudine at two dose levels in patients attending a HIV Comprehensive Care Centre in Kenya. Data were collected retrospectively from the records of 810 adult patients. Fewer stavudine related adverse effects were seen in patients ≥ 60 kg treated with 30 mg stavudine compared to those who received 40 mg (4.2 vs 16.7%, p < 0.001). Patients < 60 kg were more likely to experience drug toxicity than those ≥ 60 kg when given 30 mg stavudine (12.8 vs 4.2%, p < 0.001). Occurrence of any adverse drug reaction was significantly associated with severe immunosuppression (HR =1.45, CI: 0.86 - 2.45, p < 0.001), co-morbidities (HR = 2.16, CI: 1.06 - 4.38, p < 0.001) and treatment with isoniazid (HR = 2.07, CI: 1.09 - 3.96, p < 0.001). The onset of drug related toxicities was principally in the first year of commencing therapy. Similar immunologic outcomes were demonstrated across all the treatment groups with median CD4 cell counts after 12 months of treatment more than doubling for patients in all the study cohorts. The findings support the use of combination antiretroviral therapy regimens containing low dose stavudine in Kenya.

Key words: Low -dose stavudine, combination antiretroviral therapy, HIV, stavudine tolerability.

INTRODUCTION

Stavudine- containing combination antiretroviral therapy (cART) regimens are currently the most preferred first-line for HIV treatment in Kenya and sub-saharan Africa (Renaud-Thery, 2007). cART has led to a tremendous decrease in AIDS-related morbidity and mortality and a significant improvement in the quality of life of HIV-infected individuals in developing countries (Boyd, 2009). Suppression of viral replication by cART improves CD4 cell counts, promotes recovery from opportunistic infections and reduces the risk of new infections (Bartlett et al., 2006).

However, highly active antiretroviral therapy (HAART) is associated with adverse effects that compromise sustainability of long term therapies. The importance of treatment-related adverse effects is underscored by studies demonstrating that 40 % or more patients on antiretroviral therapy will have one or more forms of drug toxicity, and may consequently need to modify their treatment regimen during the first year of treatment (Fellay et al., 2001). According to a recent study, up to 78.4% of patients in Kenya alter their treatment regimen within 12 months of commencement of therapy mainly due to ART related toxicities (Hawkins et al., 2007).

Common short term and long term safety concerns with HAART regimens include peripheral neuropathy, lipodystrophy, anaemia and hepatotoxicity. Other adverse effects are diarrhoea and rash (Carr and Amin, 2009). In sub-saharan Africa, only a few drugs are responsible for the majority of toxicities because only limited choices exist for first-line regimens due to economic constraints. Even though stavudine based cART regimen is the most common first-line in most developing countries, many patients undergoing stavudine treatment experience adverse effects thus hampering treatment durability.

In 2007, the WHO revised its antiretroviral treatment guidelines and recommended that stavudine should be administered at lower doses; that is 30 mg twice daily for all adults down from the previous dosage of 40 mg twice

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daily for patients weighing over 60 kg (WHO, 2007).

Recently, there have been questions whether stavudine, even with dose adjustments, will bring any improvement on toxicity with some researchers and clinicians urging that it should be abandoned altogether, even in resource poor settings, in favour of other treatment alternatives (Brinkman, 2009).

Current guidelines recommending stavudine dose reduction from 40 - 30 mg were implemented as a means of improving safety parameters, using an evidence base mainly from settings outside sub-saharan Africa (Hill, 2007). It is therefore essential that the clinical and immunological efficacy of the low dose stavudine based regimens be established in African settings.

Retrospective reviews have been widely applied in the investigation of the tolerability and durability of HAART regimens. Willig et al. (2009) have showed that weight < 60 kg and low CD4 cell counts are associated with higher zidovudine toxicity through a retrospective study. Equally, in a Rwandese study, Lowrance et al. (2009) perfomed a retrospective cohort analyses that revealed excellent 6 and 12 month retention and immunologic outcomes in patients enrolled in ART program. A similar approach was adopted in this study where we undertook to compare the tolerability and efficacy of low dose (30 mg) stavudine with the previous standard dose (40 mg) at an urban setting in Kenya to ascertain whether there were any improvements on toxicity and no compromise on immunological and clinical outcomes.

METHODS

Ethical considerations

This study was approved by the University of Nairobi and the Kenyatta National Hospital Ethical Institutional Review Board.

Study site

Kenyatta National Hospital located in Nairobi, Kenya, is the largest hospital in Kenya and has a Comprehensive Care Centre (CCC) that offers basic care and antiretroviral therapy to HIV infected individuals.

Study population

All HIV-infected adults initiated on treatment with stavudine based HAART regimen between January, 2006 and December, 2008 were eligible for the study.

Study design

The design was an analytic retrospective cohort study that involved examination of records of patients on antiretroviral therapy. The 3 study arms were: patients weighing ≥ 60 kg receiving 40 mg BD stavudine; patients weighing ≥ 60 kg receiving 30 mg BD stavudine; and patients weighing < 60 kg receiving 30 mg BD stavudine. A minimal sample size of 235 patients per group was calculated to be sufficient to detect a 15% difference in the incidence of peripheral neuropathy across the groups with a power of 80% and at a two sided level of significance of 5%.

Inclusion criteria

Both male and female patients were eligible for inclusion in this study if they were adults aged at least 18 years with confirmed HIV infection and were ART- naïve at initiation of CART. “ART-naïve” was defined as never having been treated with any antiretroviral which can be used as a component of HAART. In addition eligible patients had to be on standard first-line stavudine-containing ART regimens.

Exclusion criteria

Patients were excluded if they were under 18 years of age; were receiving treatment with cytotoxic anticancer agents; were undergoing radiotherapy; were receiving immunosuppressants at the time of starting cART. Females were excluded if they were pregnant. Patients were also excluded if they were ART-experienced or were on HAART regimens that did not include stavudine.

Patient assessment

Physicians and clinical officers at the Comprehensive Care Centre (CCC) are trained and apply the WHO and Kenyan guidelines in the care of patients diagnosed with HIV. Data relating to patients demographics: age, gender, weight; disease stage: CD4 cell count, AIDS-defining illnesses, opportunistic infections, neoplasms; Co-morbidities such as TB; treatment history and adverse drug events are routinely entered in individual patient’s records.

In addition, trained pharmacists use the Daily Activity Register or the ART-dispensing tool, which is a computer software provided by Management Sciences for Health (MSH, USA) that captures demographic and drug-related information on patients receiving ARVs at the CCC. It contains the patient name and number, age, sex, ARV and other drugs dispensed, quantities dispensed, date of ART initiation and ARV refill dates.

Outcomes

Analysis was carried out on retrospective data. Regimen switch was defined as substitution of stavudine for another drug or a complete change to a second-line HAART regimen. Dose reduction was not considered as regimen switch. Lipodystrophy and peripheral neuropathy were considered as adverse drug reactions. Factors that can contribute to drug toxicities such as TB therapy were evaluated. Immunologic outcomes were measured using CD4 count changes over the treatment period. Clinical outcomes were assessed by diagnosis of opportunistic infections (OIs) or AIDS-defining illnesses over time.

Statistical analysis

An analysis of the patients’ treatment database showed that 810 patients met the study inclusion criteria and all were included in this study.

Qualitative variables were described in frequencies or percent-tages and compared between groups using Chi square (χ^2) test. Quantitative variables were described with medians or means and compared between groups using Wilcoxon rank sum test. Cox proportion hazard regression modeling was used to determine

Table 1. Baseline characteristics of the study population.

Treatment group		Stavudine 40 mg, Weight ≥60 kg	Stavudine 30 mg, Weight ≥60 kg	Stavudine 30 mg, Weight <60 kg
No. (%)		**287 (35.4)**	**238 (29.4)**	**285 (35.2)**
		Demographics		
Gender -female		150 (52.2%)	128 (53.8%)	201 (70.5%)
Median age (range)		38 (20-68)	38 (19-62)	37 (18-66)
Median weight, kg (range)		67 (60-108)	64 (60-127)	51 (31-59)
Median CD4 cell count, (range)		127 (2-373)	119.5 (1-454)	109.5 (1-366)
CD4 cell count < 100 cell/mm^3		112 (39%)	100 (42%)	138 (48.4%)
Active OI		152 (53%)	72 (25.1%) (30.2%)	165 (57.9%)
TB treatment:	Isoniazid +pyridoxine	50 (17.4%)	62 (21.8%)	42 (17.6%)
	Isoniazid only	9 (3.1%)	9 (3.2%)	6 (2.5%)
AIDS symptoms		43 (15%)	6 (2.5%)	35 (12.3%)
OI prophylaxis:	Co-trimoxazole	274 (95.5%)	269 (94.4%)	231 (97.1%)
	Fluconazole	52 (18.1%)	65 (22.8%)	42 (17.6%)
WHO STAGE:	I	53 (18.5%)	17 (6%)	33 (13.9%)
	II	88 (30.7%)	65 (2.8%)	87 (36.6%
	III	106 (36.9%)	14 (51.2%)	78 (32.8%)
	IV	40 (13.9%)	57 (20%)	40 (16.8%)
Other diseases (Renal, liver, diabetes)		4 (1.2%)	5 (2.1%)	9 (3.1%)
Anaemia		40 (13.9%)	16 (6.7%)	96 (33.7%)
Alcohol use		39 (13.6%)	19 (8%)	21 (7.4%)
		Antiretroviral regimens		
Stavudine 30 mg + Lamivudine + Nevirapine		-	79 (33.2%)	149 (52.3%)
Stavudine 30 mg + Lamivudine +Efavirenz		-	159 (66.8%)	136 (47.7%)
Stavudine 40 mg + Lamivudine + Nevirapine		157 (54.7%)	-	-
Stavudine 40 mg + Lamivudine +Efavirenz		130 (45.3%)	-	-

Abbreviations: OI, Opportunistic infections; TB, Tuberculosis.

variables that predicted the outcomes. The time to event analysis was estimated using the Kaplan–Meier product limit method. Statistical analyses were performed using SPSS software, version 13 (SPSS Inc. Chicago, USA).

RESULTS

Patients' baseline characteristics

There were 2,377 patients started on stavudine-based first-line antiretroviral therapy between January, 2006 and December, 2008 at the Comprehensive Care Centre, Kenyatta National Hospital. A total of 810 patients were included in this study. Patients were excluded for the following reasons: 131 patients had pre-existing peripheral neuropathy, 413 did not have baseline CD4 cell counts or weight, 396 were non-naïve to ART, 302 had received ART for less than 6 months, 28 were on immunosuppressive therapies, 63 patients were aged less than 18 years and file records for 234 patients could not be traced. The baseline characteristics for the 810 patients are summarized in Table 1.

There was relatively high proportion of women particularly in the group of patients treated with 30 mg stavudine weighing < 60 kg (70.5%, $p < 0.001$). The other two comparator groups, patients ≥ 60 kg receiving 30 mg or 40 mg of stavudine, had a more balanced gender distribution (52.2 and 53.8% of females respectively). Age was evenly distributed across the study groups with the median age of 37 and 38 for patients < 60 and ≥ 60 kg respectively.

The study population generally had low CD4 cell counts, indicative of severe immunosuppression, with median baseline counts for all groups under 200 cells/mm^3.

Baseline anaemia was more common in the group of patients weighing < 60 kg treated with 30 mg stavudine (33.7%, $p < 0.001$). This study arm also had the highest proportion of patients on TB treatment or isoniazid preventive treatment.

Efavirenz based regimens were more common in patients treated with 30 mg stavudine weighing more than 60 kg (66.8%, $p < 0.001$) while most patients taking alcohol (13.6%, $p < 0.001$) were in the treatment group

Table 2. Incidence of ART-induced adverse effects.

Adverse effect	n (%)	Median time to onset (range) in months
Peripheral neuropathy	167 (20.5)	6 (1 - 39)
Lipodystrophy	116 (14.3)	23 (1 - 39)
Hepatotoxicity	11 (1.3)	5 (1 – 15)
Rash	9 (0.1)	1 (1 – 9)
Nephrotoxicity	1 (<0.1)	4
Diabetes mellitus	1 (<0.1)	3

receiving 40 mg stavudine.

Safety of stavudine containing regimens

In total, there were 167 episodes of peripheral neuropathy and 116 of lipodystrophy in 260 (32.1%) patients. The cumulative incidences of adverse effects were 11% at 6 months and 18% at 12 months. Peripheral neuropathy was the highest reported toxicity accounting for 66.8% of the toxicities. The median time to development of any clinical toxicity was 9 months (1 - 36 months). The incidences of the adverse drug reactions by antiretroviral regimen are as shown in Table 2. Patients weighing more than 60 kg treated with 30 mg stavudine experienced fewer adverse effects compared to those treated with 40 mg stavudine in the same weight category (4.2 vs 16.7%, $p < 0.001$). In patients treated with 30 mg stavudine, those weighing less than 60 kg had a higher incidence of adverse effects than those weighing more than 60 kg (12.8 vs 4.2%, $p < 0.001$).

Occurrence of any adverse drug reaction was significantly associated with treatment with 30 mg stavudine in patients weighing less than 60 kg (HR = 2.87, CI: 1.65 - 4.08, $p < 0.001$), treatment with 40 mg stavudine (HR = 3.91, CI:2.29 - 6.66, $p < 0.001$,) age greater than 45 years (HR = 2.16, CI:1.41 - 3.31, $p < 0.001$), co-morbidities (HR = 2.16, CI:1.06 - 4.38, $p < 0.001$), treatment with isoniazid (HR = 2.07, CI:1.09 - 3.96, $p < 0.001$) and severe (WHO stage IV) immunosuppression (HR = 1.45, CI:0.86 - 2.45, $p < 0.001$).

For all groups, the onset of peripheral neuropathy was mainly during the first year of treatment. A total of 127 (76%) cases of peripheral neuropathy were diagnosed within the first year of treatment, 18.6% occurred during the second year of treatment with only 8 (4.8%) new cases during the third year of treatment.

The probability of remaining free of any adverse drug reaction or peripheral neuropathy (Figures 1 and 2) was higher in patients treated with 30 mg stavudine weighing more than 60 kg compared to those treated with 40 mg stavudine and patients weighing less than 60 kg on 30 mg stavudine.

Most cases of peripheral neuropathy (123, 73.7%) were categorized as mild, with only 10 (1.2%) cases being categorized as severe (grade III) in initial presentation. Moderate (grade II) peripheral neuropathy was observed in 34 (42%) of the patients. No patient was reported to have incapacitating (grade IV) peripheral neuropathy at the time of initial diagnosis. While slightly more females experienced this adverse effect compared to males (11.9 vs 8.5%), this difference was not significant. Severe (grade III) peripheral neuropathy was associated with use of 40 mg stavudine ($p < 0.001$) and age greater than 40 years ($p = 0.05$).

The proportion of patients remaining free of lipodystrophy (Figure 3) was higher in patients receiving 30 mg stavudine and weighing above 60 kg compared to those treated with 40 mg stavudine.

Univariate analysis revealed higher hazard rates for lipodystrophy with 40 mg stavudine (HR-31.1, CI: 7.6-127.4, $p < 0.001$), treatment with 30 mg stavudine in patients weighing less than 60 kg (HR = 17.3, CI: 4.2 - 72, $p < 0.001$) and presence of baseline co-morbidities such as liver disease, renal disease and diabetes mellitus at initiation of ART (HR = 3.55, CI: 1.44 - 8.76, $p = 0.006$). Lipodystrophy met criteria for a severe event at initial presentation in 30 (25.9%) patients. Most of the cases (85, 73.3%) were categorized as moderate with only one patient presenting with mild (grade I) lipodystrophy. On multivariate analysis, no baseline characteristics were found to lead to increased risk of experiencing lipodystrophy. More females (79, 68.1%) experienced this adverse effect (HR = 0.52, CI: 0.33 - 0.82, $p = 0.005$).

Other clinical toxicities reported included hepatotoxicity (12, 1.5%) rash (9, 1.1%), nephrototoxicity 1(0.1%) and diabetes mellitus 1(0.1%).

Immunologic outcomes

Significant improvements in CD4 cell counts were observed in all the treatment groups. During the first year of treatment, the overall mean CD4 cell counts were 201, 253, 269 and 297 at 3, 6, 9 and 12 months respectively. There was no significant difference in the CD4 counts in patients treated with 30 mg stavudine weighing more than 60 kg and those with similar weights treated with 40 mg stavudine (309 vs 293, $p = 0.37$). However, mean CD4 counts in patients weighing less than 60 kg treated with 30 mg stavudine were lower than those weighing

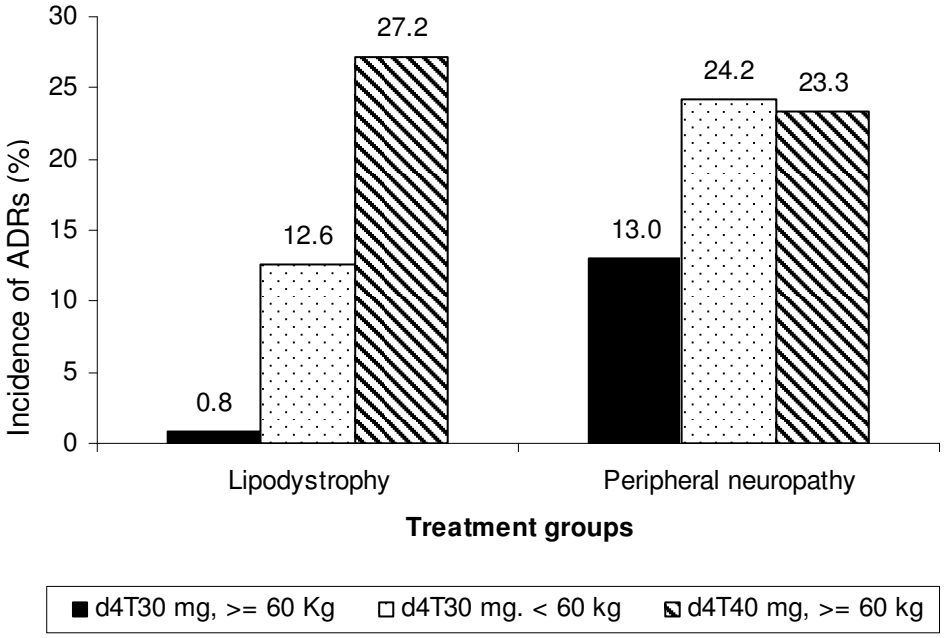

Figure 1. Incidence of stavudine-induced adverse effects.
Abbreviations: ADRs, Adverse drug reactions, d4T30 mg > = 60 Kg, patients weighing ≥ 60 kg and taking 30 mg stavudine-based regimens; d4T30 mg < 60 kg, patients weighing < 60 kg and taking 30 mg stavudine-based regimens; d4T40 mg > = 60 Kg, patients weighing ≥ 60 kg and taking 40 mg stavudine-based regimens.

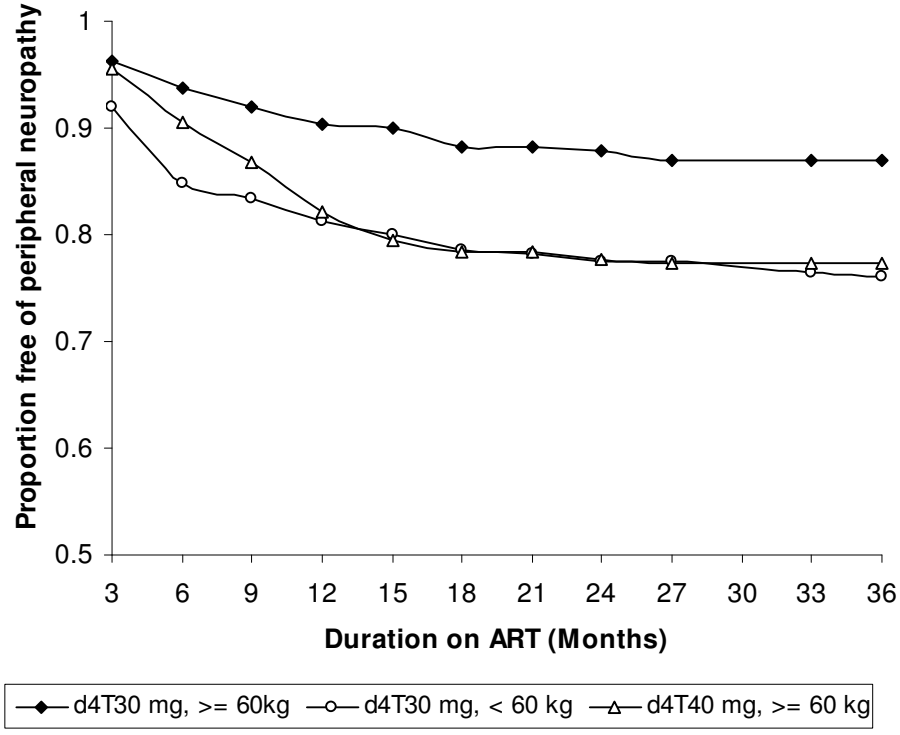

Figure 2. Probability of remaining free of peripheral neuropathy.
Abbreviations: ART, Antiretroviral therapy, d4T30 mg > = 60 kg, patients weighing ≥ 60 kg and taking 30 mg stavudine-based regimens; d4T30 mg < 60 kg, patients weighing < 60 kg and taking 30 mg stavudine-based regimens; d4T40 mg > = 60 Kg, patients weighing ≥ 60 kg and taking 40 mg stavudine-based regimens.

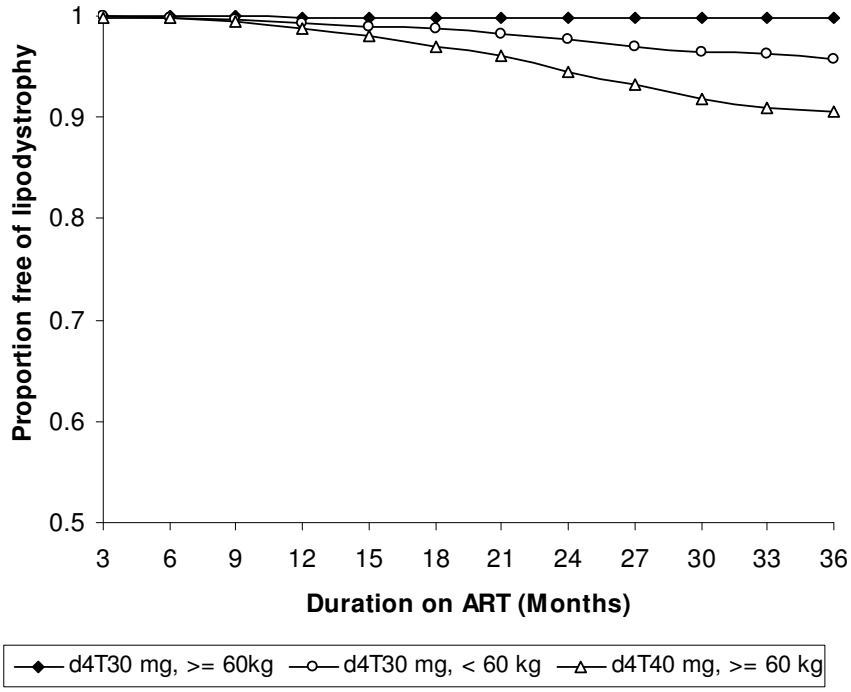

Figure 3. Probability of remaining free of lipodystrophy.
Abbreviations: ART, Antiretroviral therapy, d4T30 mg > = 60 Kg, patients weighing ≥ 60 kg and taking 30 mg stavudine-based regimens; d4T30 mg < 60 kg, patients weighing < 60 kg and taking 30 mg stavudine-based regimens; d4T40 mg > = 60 Kg, patients weighing ≥ 60 kg and taking 40 mg stavudine-based regimens.

more than 60 kg (286 vs 309, p = 0.002).

Clinical outcomes and opportunistic infections

A significant decrease in occurrence of opportunistic infections (OIs) was recorded across all treatment groups. Overall there was a decrease in occurrence of all opportunistic infections with incidences of 1.3% at 3 months and 0.7% at 12 months compared to 47.4% at baseline. The incidence of AIDS- defining illnesses and neoplasms decreased from 10.4% at baseline to less than 1% by the first month of treatment.

Development of new OIs occurred in 149 (18.4%) patients with a median time on therapy of 3.5 months (1 - 17 months).The cumulative incidences of new OIs were 9.6% and 11.4% at 6 and 12 months respectively. The OIs reported in order of frequency were pulmonary TB (34, 4.2%), candidiasis (29, 3.6%), herpes simplex (11, 1.35%), herpes zoster (9, 1.1%), Karposi's sarcoma and cryptococcal meningitis (8 cases each, 1%), *Pneumocystis* pneumonia (6, 0.7%), extrapulmonary tuberculosis, chronic diarrhea and toxoplasmosis (3 cases each, 0.3%), lymphoma and cervical cancer (1 case each, 0.1%).

The risk of getting a new opportunistic infection was associated with use of 40 mg stavudine (HR = 8.4,CI:3.56 - 19.7, p < 0.001), treatment with 30 mg stavudine in patients weighing less than 60 kg (HR = 6.10, CI:2.56 - 14.5, p < 0.001) and age greater than 45 years (HR = 8, CI:1.14 - 67.5, p = 0.04). Although more OIs occurred in those using alcohol, no statistical association was found. Initial presentation with severe immunosuppression was found to be the greatest risk factor for experiencing a new OI (HR = 32, CI: 4.39 - 233.5, p < 0.001). The presence of an active OI at initiation of ART was not found to be associated with onset of new OIs during therapy with stavudine.

Changes on patients' weight during treatment

The overall mean weight change at 3, 6, 9 and 12 months was 1.2, 3.7, 6.2 and 7.9 kg respectively (p = 0.04). Patients with weights below 60 kg recorded the highest weight gain (9 kg) during the first year of treatment compared to 4.3 kg in patients treated with 40 mg stavudine (p < 0.001) and 6.7 kg in the group weighing more than 60 kg receiving 30 mg stavudine (p = 0.004).

DISCUSSION

This study was conducted in ART naïve HIV –infected

patients primarily to generate clinical safety and efficacy data for 30 mg stavudine -based regimens in an urban setting in Kenya's largest hospital.

The study was adequately powered and the proportions of patients receiving 30 or 40 mg were similar in ≥ 60 kg category. Median CD4 counts (119.5 vs 127 cells/mm^3), age (both 38 years) and gender distribution (53.8 and 52.2% females) were also broadly similar across the two comparator groups. A third category of patients was included to assess the performance of 30 mg stavudine in patients with lower weights (< 60 kg). Patients in this latter category had more severe immunosuppression (109.5 median CD4 cells/mm^3), significantly more females (70.5%) and more active opportunistic infections (58%) at baseline.

The results demonstrated similar outcomes in efficacy across the different treatment groups with median CD4 cell counts after 12 months of treatment, more than doubling to 309 and 293 cells/mm^3 for 30 and 40 mg groups ≥ 60 kg respectively. Comparable outcomes were found with the < 60 kg group where the median CD4 cell counts increased 2.6 fold to 286 cells/mm^3. These findings are consistent with studies outside sub-saharan Africa (Ait-Mohand et al., 2008; Wolf et al., 2004) that showed low and moderately high dosages of stavudine have similar efficacy outcomes.

Adverse drug events were registered in all treatment groups at varying incidence and severity. In general, 18% of patients had experienced drug toxicity at 12 months of treatment. The finding is in agreement with a recent study conducted in western Kenya which found prevalence of toxicities leading to treatment discontinuation or changes at 20% (Braitstein et al., 2009), but does not accord with another study in Nairobi that estimated such prevalence at 78.4% (Hawkins et al., 2007).

It is notable that even though peripheral neuropathy was the most common toxicity, patients who were ≥ 60 kg receiving 30 mg stavudine were 4 times less likely to experience this event when compared to those receiving 40 mg stavudine. Indeed the most severe cases of peripheral neuropathy were seen in the group receiving 40 mg. This finding supports the WHO recommendation to step down stavudine dose to reduce stavudine toxicity while retaining efficacy (WHO, 2007).

In contrast, patients < 60 kg receiving 30 mg stavudine experienced more toxicities than all the other treatment groups. This brings to the fore the question whether stavudine dose should be stepped down further for this weight category. In deed some studies have reported that efficacy would not compromised by reducing stavudine dose to 20 or 15 mg BID (McComsey et al., 2008).

Treatment with isoniazid was associated with development of peripheral neuropathy. As some studies have associated concomitant use of isoniazid and d4T as strong predictors of peripheral neuropathy (Breen et al., 2000), it may be recommended that such patients should be considered for alternative treatment. It was shown that severe immunosuppression increased the risk of developing adverse events. This finding is similar to that of Zhou et al (2007), where higher toxicity to stavudine was observed in Indian patients with lower CD4 cell counts. In common with the results of Affandi et al (2008), from an Indonesian cohort, older patients (>45 years) were determined to be more likely to experience d4T adverse effects.

Limitations in this study include the absence of viral load data for the patients. Viral load is a superior indicator for HAART efficacy than immunologic or clinical indicators. It would be highly desirable for sub-Saharan African countries to introduce viral load testing for all patients receiving HAART. As data were not gathered on patients' ethnic status nor with regard to the genetic make up of individual patients, inter-ethnic or inter-individual differences cannot be inferred. Further studies in different African countries are also recommended. It was also noted that patients weighing < 60 kg presented at later stages of the disease than those in the higher weight category. It is therefore possible that the higher toxicities observed for stavudine was in part due to the underlying advanced disease status.

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