

Research Article

Is it Time to Abandon Stavudine? The Safety and Tolerability of Low Dose Stavudine versus Zidovudine in Urban Kenya

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Background: Stavudine (d4T) and zidovudine (AZT) form the backbone of the most commonly used first-line highly active antiretroviral therapy (HAART) regimens in Kenya. In 2012, more than 60 % of patients undergoing combination antiretroviral therapy were either on AZT or d4T based regimens, mainly due to their affordability and availability in fixed dose combinations. Following the World Health Organization's recommendation in 2010 that d4T should be phased out due to safety concerns, Kenya has been steadily withdrawing d4T from HIV/AIDS treatment programmes. Despite these decisions, questions as to whether stavudine ought to be altogether abandoned in resource constrained settings continue to elicit debate among clinicians, researchers and patient groups.

Objective: This study was consequently designed to compare the tolerability and efficacy of AZT with low dose d4T in treatment of HIV infected adults in urban Kenya, and to generate data on the safety of low dose stavudine.

Method: The design was an analytic retrospective hospital-based cohort study that involved examination of records of patients on antiretroviral therapy. The study had two comparator arms: (i) ART-naive adult patients initiated on stavudine 30 mg based HAART, and (ii) ART-naive adult patients initiated on zidovudine based HAART. Quantitative variables were described with medians or means, and compared between groups using Wilcoxon rank sum test. Association effects were determined by use of Chi-square test. Categorical variables were summarized using proportions. The time to event analysis was estimated using the Kaplan-Meier product limit method. Cox Proportional Hazards regression was used to model the hazard rates of regimen switching.

Results: The incidence rate (IR) of switching regimen was higher in patients initiated on zidovudine than in patients initiated on low dose stavudine (11.3 % and 7.0 % respectively). The most common reason for regimen switch was toxicity (79.2 %). In patients initiated on stavudine, lipodystrophy was the main reason for treatment change (53.2 %) followed by peripheral neuropathy (23.4 %). Amongst patients initiated on zidovudine, anaemia was the main reason for treatment change (33.3 %). There was no significant difference in median change in CD4 cell counts between the two treatment groups.

Conclusion: The study has showed that patients initiated on a zidovudine based regimen were more likely to change their treatment compared to those on a low dose stavudine. Stavudine therefore still has its benefits, and public health programmes should not altogether abandon it.

Keywords: Stavudine phase out, low dose stavudine, zidovudine

Received: April, 2013

Published: June, 2013

1. Introduction

Stavudine (d4T) and zidovudine (AZT) form the backbone of the most commonly used first-line highly active antiretroviral therapy (HAART) regimens in Kenya. In 2012, more than 60 % of patients undergoing combination antiretroviral therapy were either on AZT or d4T based regimens, mainly due to their affordability and availability in fixed dose combinations (NASCO, 2012).

While the use of HAART has led to a substantial reduction in mortality and morbidity, as well as enhancement of quality of life of HIV-infected persons, HAART is associated with diverse adverse drug reactions that limit the sustainability of long term treatment (Boyd, 2009).

Safety concerns with stavudine are well documented and include lipodystrophy, peripheral neuropathy and other mitochondrial toxicities (Carr and Amin, 2009). Zidovudine-related haematological toxicity is also a significant safety concern (Carr and Amin, 2009).

Stavudine-related toxicities have led to various recommendations by the World Health Organization (WHO): in 2007, the WHO recommended dose reduction of d4T from 40 mg twice daily (BD) to 30 mg twice daily for all adults (WHO, 2007); and in a subsequent guideline of 2010, the WHO recommended that d4T should be phased out in all countries (WHO, 2010). Kenya has adopted the WHO recommendations, and is currently phasing out stavudine in favour of tenofovir.

Despite the decision by public health authorities to replace d4T in HIV/AIDS management programs, the question as to whether stavudine ought to be altogether abandoned in resource constrained settings continues to elicit debate. Discordant voices have arisen among clinicians, researchers and patient groups over the issue (Innes, 2011; Andrieux-Meyer, 2012; Venter, 2012). While the proponents of total stavudine phase out insist that the safety concerns with stavudine trump all considerations as to its cost-effectiveness, the sympathizers of d4T retention point out that the safety data relied upon to argue for stavudine withdrawal are based on findings from studies with high dose (40 mg BD) stavudine. To buttress their arguments, some d4T advocates insist that the budgetary constraints in resource limited countries need to be taken into account, in order to attain the goal of supporting treatments for all those who need it, and that low dose d4T should still have a role in combination antiretroviral therapy (cART). This is even more so as the external sources of funds such as the US PEPFAR funding, that have supported many African HIV/AIDS care programmes, are already being scaled down in some African countries, and these economies will therefore have to find alternative financial means or source funds from within, to support treatment.

This study was consequently designed to compare the tolerability and efficacy of AZT with low dose d4T in treatment of HIV infected adults in urban Kenya, and to generate data on the safety of low dose stavudine.

2. Methods

2.1 Ethical considerations

This study was approved by the Kenyatta National Hospital and University of Nairobi Ethics and Research Review Committee (KNH/UoN ERC, Approval Reference No. P/306/11/2009).

The review of patient files was done within the Kenyatta National Hospital Medical Records Department to ensure confidentiality. Patient names were not included in the data collection forms. Patients were also assigned study numbers in the data collection forms instead of their hospital admission numbers.

2.2 Study area

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

2.3 Study population

All ART-naive, HIV-infected adult patients started on standard first line cART regimens containing zidovudine or low dose stavudine between January 2008 and January 2009 were eligible for the study.

2.4 Study design

The design was an analytic retrospective hospital-based cohort study that involved examination of records of patients on antiretroviral therapy. The study had two comparator arms: (i) ART-naive adult patients initiated on stavudine 30 mg based HAART, and (ii) ART-naive adult patients initiated on zidovudine based HAART. A minimal sample size of 152 patients per group was calculated to be sufficient to detect incidence rates of regimen switch of 40 % in patients initiated on stavudine and 25 % in patients initiated on zidovudine at a two sided level of significance of 5 % and 95 % level of confidence.

Inclusion criteria

Both male and female patients were eligible for inclusion in the study if they were adults aged at least 18 years with confirmed HIV infection and were ART-naive at initiation of cART. 'ART-naive' was defined as never having been treated with any antiretroviral drug which can be used as a component of cART.

In addition eligible patients had to be on standard first-line zidovudine or stavudine-containing ART regimens for at least 6 months.

Exclusion criteria

Patients were excluded if they were under 18 years of age; were receiving treatment with immunosuppressive agents; were undergoing anticancer or radiotherapy treatment 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 zidovudine or stavudine.

Table 1: Baseline characteristics of the study population in the two study arms

Baseline characteristics	d4T Group‡ (d4T30 mg +3TC+EFV/NVP)		AZT Group (AZT+3TC+EFV/NVP)		P value
	No. (%)	(n=238)	No. (%)	(n=277)	
Demographics					
Female	169	71.0 %	166	59.9 %	0.009*
Median age (range)	238	35 (18 – 88)	277	35 (18 – 65)	0.850
Age ≥40 years	69	29.0 %	85	30.7 %	0.675
HIV Infection					
Median baseline CD4 cell count, /mm ³	238	153 (3 - 2211)	277	173 (1 – 671)	0.270
Baseline CD4 cell count <100 cells/mm ³	77	32.4 %	81	29.2 %	0.445
Median baseline weight, kg (range)	238	58 (35-118)	277	61 (35-96)	<0.001*
Baseline weight <60 kg	129	54.2 %	113	40.8 %	0.002*
Median baseline MCV, fl (range)	238	84 (5 - 116)	277	84 (8 - 116)	0.177
Baseline MCV, fl:					
< 80	82	34.5 %	64	23.1 %	
80 – 100	141	59.2 %	197	71.1 %	0.013*
> 100	15	6.3 %	31	5.8 %	
AIDS symptoms	12	5.0 %	21	7.6 %	0.241
TB	24	10.1 %	36	13.0 %	0.304
TB Treatment: Isoniazid + Pyridoxine	10	4.2 %	27	9.7 %	
Isoniazid only	14	5.9 %	9	3.2 %	0.046*
Baseline WHO stage: I	10	4.2 %	17	6.1 %	
II	70	29.4 %	97	35.0 %	
III	118	49.6 %	119	43.0 %	0.328
IV	40	16.8 %	44	15.9 %	
Concurrent medical conditions					
Co-morbidities (Renal, Diabetes, Hypertension, Hepatitis B)	6	2.5 %	5	1.8 %	0.575
Anaemia: Hb < 11	74	31.1 %	44	15.9 %	<0.001*
Alcohol use	17	7.1 %	8	2.9 %	0.025*
Antiretroviral regimens					
NVP	101	42.4 %	119	43.0 %	
EFV	137	57.6 %	158	57.0 %	0.905

* - Significant at $P < 0.05$; ‡ All subjects in the d4T treatment arm took d4T 30 mg

Patient assessment and Case Definitions

Physicians, medical and clinical officers at the KNH 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; comorbidities 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 (DAR) 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

The primary measure of tolerability was regimen switch, defined as substitution of stavudine or zidovudine for another drug, a complete change to a second-line HAART regimen or a complete discontinuation of HAART.

The primary measure of immunological efficacy was the CD4 cell counts. The changes in CD4 cell counts were compared across the two study groups. Isoniazid was used as a surrogate marker for the treatment of tuberculosis. The secondary outcomes for efficacy were

occurrence of HIV/AIDS defining illnesses. Haemoglobin level post HAART initiation was a clinical outcome while ADRs resulting in regimen switch and time to regimen switch due to ADRs were used as secondary outcomes for tolerability. The dependent variables were the CD4 cell counts, weight, age, WHO stage and AIDS-defining illnesses at baseline. The independent variables were the HAART regimen initiated. The confounders for experiencing regimen switch were duration of therapy, CD4 counts less than 100 cells/mm³, low body mass index (<18 kg/m²), concomitant use of other neurotoxic drugs, age >40 years, other co-morbidities and use of alcohol.

2.5 Statistical Analysis

Qualitative variables were described in frequencies or percentages and compared between groups using Chi square (χ^2) test. Man Whitney U test was used to compare continuous variables between two groups while Kruskal Wallis test was used to compare between more than two groups. Pearson's Chi-square test was used to test for the strength of association between categorical variables.

Quantitative variables were described with medians or means, and compared between groups using Wilcoxon rank sum test. Categorical variables were summarized using proportions. The time to event analysis was estimated using the Kaplan-Meier product limit method.

Cox Proportional Hazards regression was used to model the hazard rates of regimen switching at 6, 12, 18 and 24 months. Hazard rates were compared across different levels within a single variable where one level was used as the reference category. Hazard ratios were used to measure the number of times regimen switch was experienced in one category of a single variable compared to the reference category.

A parsimonious model was developed using variables previously tested individually and confirmed to relate significantly with the outcome variable (regimen switching) at bivariate analysis. These techniques assisted to identify potential confounders and effect modifiers and as a result establish independent predictors of regimen switching among the study participants. Level of significance was fixed at 0.05 ($p < 0.05$) with a 95% confidence interval.

Statistical analyses were performed using SPSS software, version 13 (SPSS Inc. Chicago, USA).

3. Results

Baseline characteristics of the study population

There were 2,435 adult patients initiated on either zidovudine or low dose stavudine based first-line antiretroviral therapy between January 2008 and January 2009, at the Comprehensive Care Centre, Kenyatta National Hospital. A total of 515 patients were included in this study. Patients were excluded for the following reasons: 292 were non-naïve to ART, 620 had been on therapy for less than 6 months, 860 did not have baseline CD4 cell counts, and the file records for 148 patients could not be traced. The baseline

characteristics for the 515 patients are summarized in **Table 1**.

The majority of the study patients were females accounting for 65.4 %. The median age for all the patients was 35 (18-88) years with 155 (30.1 %) aged more than 40 years. At the start of therapy, 158 (30.7 %) patients had CD4 cell count less than 100 cc/mm³. Median bodyweight at baseline was 60 (35 -118) kg with 273 (53.0 %) weighing more than 60 kg. Median MCV was 84 (50-116) fl. Majority of the patients (46.0 %) initiated treatments at WHO stage III disease and 511 (99.2 %) were on prophylactic co-trimoxazole. There were 60 (11.7 %) patients on TB treatment at baseline and 33 (6.4 %) patients had AIDS defining symptoms while anaemia was present in 118 (22.9 %) patients.

Distribution of the patients initiated on d4T and AZT based regimens was comparable, with 277 (53.8 %) patients started on AZT based regimens. Patients treated with low dose d4T regimen had the highest proportion of females (71.0 %) compared to those treated with AZT regimen (59.9 %). A similar pattern was observed for baseline weight where 129 (54.2 %) of the patients on d4T weighed less than 60 kg compared to 113 (40.8 %) of those on AZT treatment ($p=0.002$). There was a difference in MCV between the two treatment arms ($p=0.013$) with the extreme categories (<80 and >100) more pronounced in patients initiated on d4T (34.5 % and 6.3 %) compared to those on AZT (23.1 % and 5.8 %).

Curiously, anaemia was more common in patients put on d4T (31.1 %) compared to those on AZT (15.9 %). There was no significant difference in the number of patients on NVP and EFV across the two study arms ($p=0.906$).

Durability on initial antiretroviral regimen

At 24 months of follow-up 40 (16.8 %) of patients on d4T were still remaining in the initial antiretroviral regimen compared to 83 patients (30.0 %) of those on zidovudine. Median durability on d4T was 12 months [95 % CI = 10.54 -13.46] and 18 months [95 % CI = 17.06 - 18.94] for AZT.

Regimen Switch

A total of 130 (25%) patients experienced regimen switches with majority of the patients initially being on d4T (72.3 %).

The main reason for regimen switch was ADRs, accounting for 79.2 % among which lipodystrophy was the most common (43.1 %). Peripheral neuropathy accounted for 20.0 % and anaemia 10.0 % of the reasons cited.

In the d4T study arm, 94 patients switched treatment because of the need to treat tuberculosis ($n = 5$), lipodystrophy ($n=50$), anaemia ($n = 1$), treatment failure ($n = 4$), peripheral neuropathy ($n = 22$), elevated triglycerides ($n = 2$), and Steven Johnson's syndrome ($n = 1$). Reasons for regimen switch were not indicated for nine patients in the d4T group (**Figure 1**).

Amongst the patients initiated on AZT based regimens, 36 patients switched because of the need to treat tuberculosis (n = 7), lipodystrophy (n=6), anaemia (n = 12), treatment failure (n =2), peripheral neuropathy (n = 4), elevated triglycerides (n = 1), and Steven Johnson's syndrome (n = 3). The reason for one regimen switch was not indicated.

Time to regimen switch between the two treatment groups

There was a significant difference in survival probabilities (probability of not switching) by treatment groups ($P < 0.001$). Median time to first regimen switch was 15 [95 % CI= 13 - 17] months for patients on d4T compared to 5 [95 % C= 3 - 7] months for patients on AZT as shown in **Figure 2**.

Cumulative time to regimen switch due to adverse drug reactions

Survival probabilities were compared between the adverse drug reactions that resulted in regimen switch, using the Log-rank test. There was a significant difference in survival experience between different cited reasons for switching regimens ($P < 0.001$). Median time to regimen switch for patients who developed lipodystrophy was 17 [95 % CI = 16 - 18] months, peripheral neuropathy was 12 [95 % CI = 10 - 14] months and those that developed anaemia was 4 [95 % CI = 3 - 5] months.

Comparison of median time to regimen switch between the two groups

Median time to regimen switch by treatment groups was not statistically different for all reasons cited (**Figure 3**). In patients who developed lipodystrophy, median time to switch was 17 [95 % CI = 15 - 19] months among patients on d4T compared to 10 [95 % CI = 0 - 22] among those on AZT ($p=0.635$). Median time to regimen switch due to peripheral neuropathy was 12 [95 % CI = 10 - 14] months in the d4T group compared to 5 [95 % CI = 0 - 13] in AZT group ($p=0.377$). Among patients who experienced treatment failure, median time to switch was 12 months for patients on d4T compared to 18 months for patients on AZT ($p=0.583$). Median time to switch due to anaemia was 18 months for patients on d4T based regimen compared to 4 months [95 % CI = 3 - 5] for patients on AZT based regimen ($p=0.076$).

Drug substitution

Majority of the 130 patients switched to tenofovir based regimens. Regimen change from AZT/3TC/EFV or d4T/3TC/EFV was due to the need to treat tuberculosis or due to Steven Johnson's syndrome. Two (2) patients initially on d4T based regimens switched to a second line regimen due to treatment failure.

Immunological outcomes

Median CD4 change from baseline increased significantly from 0 to 193 in patients initiated on d4T

($p=0.004$) and to 191 in patients initiated on AZT ($p=0.001$). Comparison of CD4 change at each time point between the treatment groups was not significantly different.

Comparison of change in weight between the two treatment groups

Median change in weight from baseline increased significantly from 0 to 6.5 in the d4T group ($P < 0.001$) and to 4 in the AZT group ($P < 0.001$). Comparison of weight change at each time point between the treatment groups was not significantly different.

Comparison of change in haemoglobin level

Median change in haemoglobin level from baseline increased significantly from 0 to 2.2 in patients on d4T ($p=0.003$) and to 4 in patients on AZT ($p=0.003$). Comparison of change in haemoglobin level between the treatment groups was significantly different at 6, 12 and 18 months, but significant at 24 months.

Change in MCV during treatment with AZT and d4T

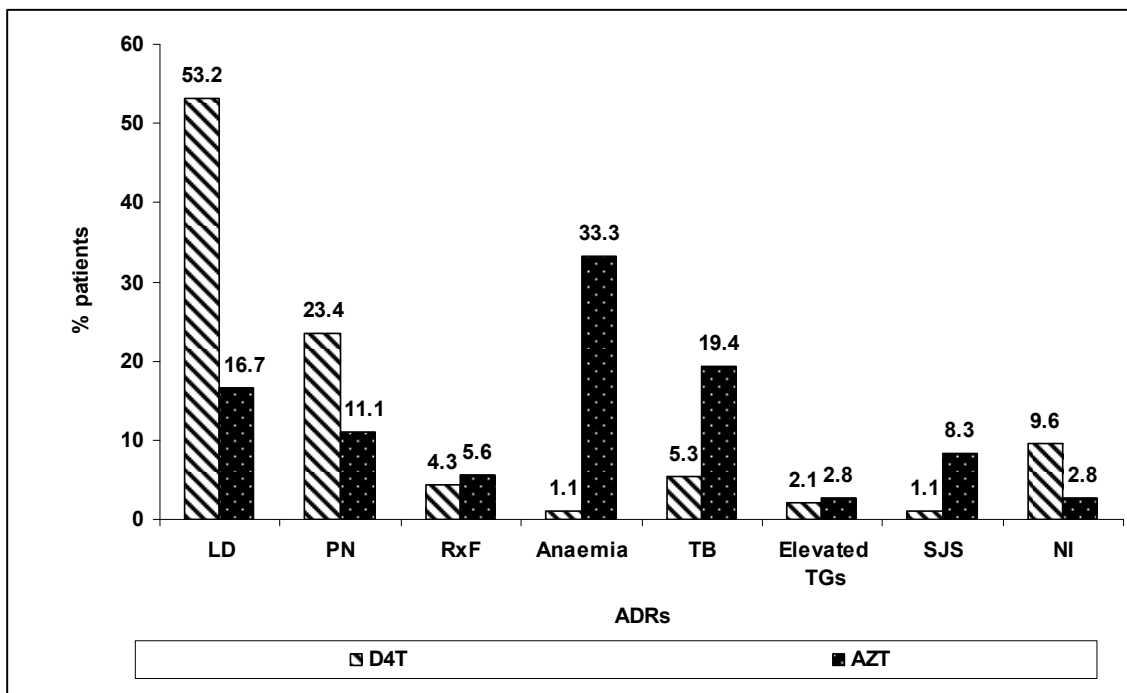
Median change in MCV from baseline increased significantly from 0 to 14 fl in the d4T group ($P < 0.001$) and to 4 in the AZT group ($p=0.001$). Comparison of Mean Corpuscular Volume change between the treatment groups was not significantly different at 6, 12 and 24 months, but significantly different at 18 months as shown in **Figure 4**.

There was a significant difference in distribution of patients with $MCV > 100$ between treatment groups at different time points ($p=0.034$). At baseline, 6 and 12 months, majority of the patients with $MCV > 100$ were on d4T but with time the trend changed to AZT for months 18 and 24.

Factors predictive of first regimen switch

Cox proportional hazard model was used to identify variables predictive of regimen switch (**Table 2**). Use of AZT based regimen was found to be the most important predictor of regimen switch. Patients treated with AZT based regimen were 2 times more likely to switch regimen compared to those treated with d4T based regimen ($p=0.001$). The incidence rate of treatment change in patients treated with AZT based regimen was 11.3 % compared to 7.0 % in patients treated with d4T.

The relationship between regimen switching and use of Isoniazid was marginally significant. Patients treated with Isoniazid were found to have a slight elevated risk of regimen switch compared to those who did not receive isoniazid (HR=1.69, CI: 0.95 - 3.00, $p=0.074$). In the parsimonious model, regimen at ART initiation and use of isoniazid were found to be predictive of regimen switching. Patients treated with AZT based regimen were still found to have a two-fold risk of experiencing regimen switch compared to those treated with d4T based regimen. Patients on isoniazid increased the risk of switching regimen 1.85 times compared to those who were not on isoniazid.



LD-Lipodystrophy, *PN*-Peripheral neuropathy, *RxF*-Treatment failure, *TB*-Treatment for tuberculosis, *TGs*-Triglycerides, *SJS*-Steven Johnson's Syndrome, *NI*-not indicated.

Figure 1: Reasons for regimen switch by treatment groups

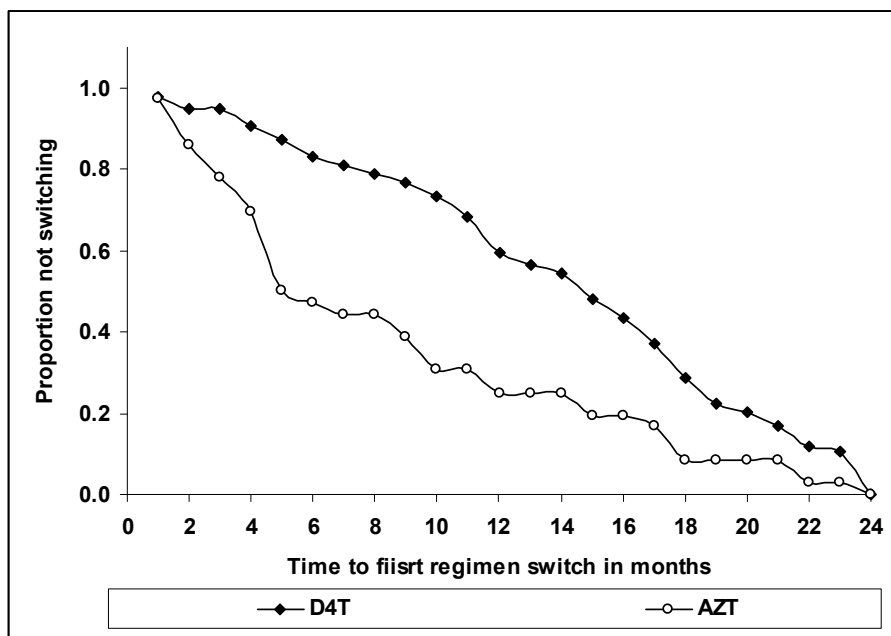


Figure 2: Survival probability to First switch by treatment groups

4. Discussion

This study was conducted in ART naïve HIV-infected patients primarily to compare clinical safety of low dose stavudine and AZT based regimens in an urban setting in Kenya's largest referral hospital. The study was adequately powered and the proportions of patients receiving d4T or AZT were comparable across the

groups. Nearly half (46 %) of the patients in this study had moderate (WHO III) immunosuppression and 22.9 % had anaemia. The high degree of immunosuppression at the initiation of HAART predisposes the patients to adverse drug effects and is also a risk factor to drug interactions due to concurrent use of drugs such as isoniazid which was being used by 11.7 % of patients who had active tuberculosis at baseline.

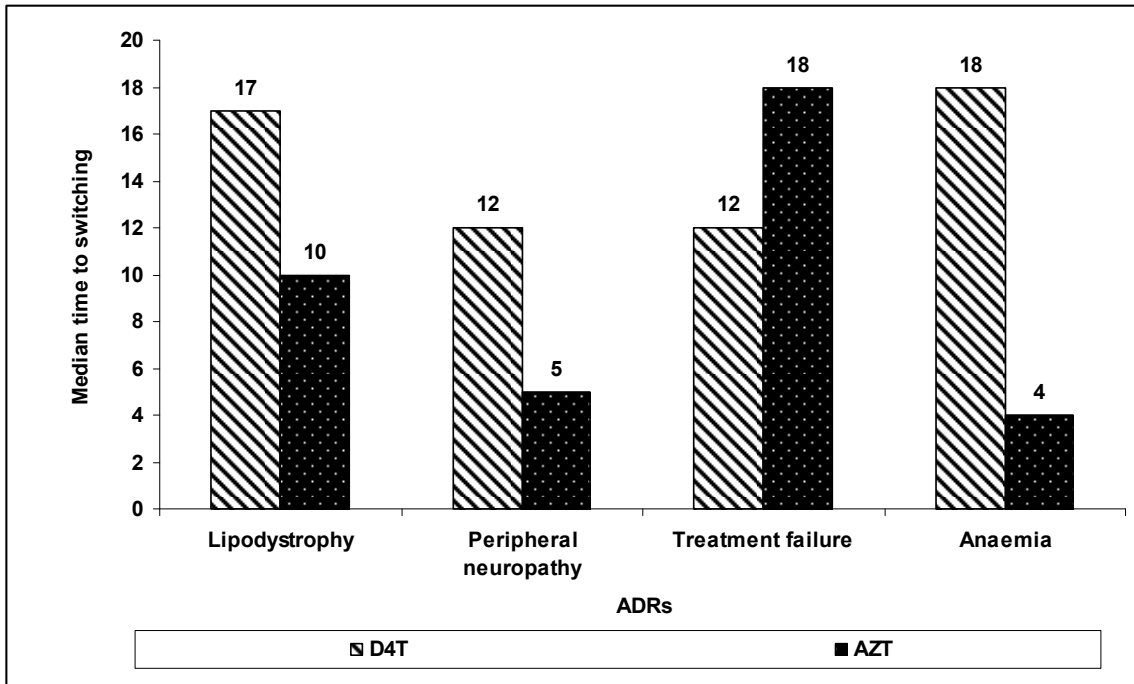


Figure 3: Median time in months to regimen switch by treatment groups

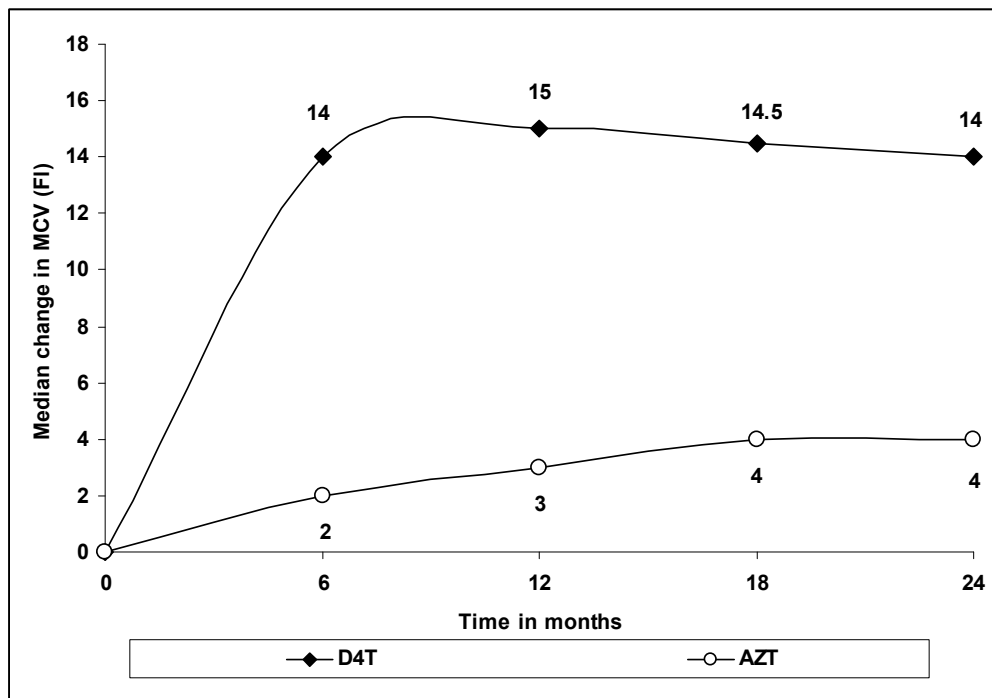


Figure 4: Median MCV change by treatment groups

Cumulatively, 25% of patients who enrolled in the study switched their initial regimens, with a higher proportion of the patients switching regimens from the stavudine arm (40 % vs 11 %). The findings accords with similar studies in Kenya. In a previous study, we found that 18 % of patients of patients had experienced toxicity at 12 months of treatment leading to regimen switching (Karara et al, 2010). Similarly, Braitstein et al

(2010) found a 20 % prevalence of toxicities leading to treatment discontinuation in western Kenya.

The incidence rate of treatment change was higher in patients initiated on zidovudine than in patients initiated on low dose stavudine (11.3 % vs. 7.0 %). The difference in prevalence and incidence rates is attributed to the shorter exposure time in patients on zidovudine compared to those on stavudine due the

shorter median time to regimen switch due to anaemia. This also accords from findings by Braitstein et al (2010) which showed that patients receiving zidovudine-based regimens were the most likely to discontinue or change regimen, while those on d4T based regimen were less likely to switch regimen.

In patients initiated on stavudine, lipodystrophy was the most common reason for treatment change (53.2 %) followed by peripheral neuropathy (23.4 %). Amongst patients initiated on zidovudine, anaemia was the main reason for treatment change (33.3 %). Treatment changes due to lipodystrophy and peripheral neuropathy were however lower in patients on zidovudine (16.7 % and 11.1 % respectively). Patients initiated on zidovudine had a shorter median time to treatment change due to lipodystrophy (10 vs. 17 months), peripheral neuropathy (5 vs. 12 months) and anaemia (4 vs. 18 months) compared to those initiated on stavudine. These rates are similar to the findings of a study in Cameroon which reported incidence rates of treatment change of stavudine and zidovudine based HAART to be 10.9 % and 12 % respectively (Laurent et al 2007) and lower than the rates (22.3 % and 31.8 %) respectively reported by Zhou et al (2007).

Significantly, lipodystrophy was the predominant cause of switches by patients on stavudine (53.2 %), a finding also supported the study by Zhou et al (2007). This finding is curious as most other studies have reported peripheral neuropathy as the main toxicity leading to change in regimen in patients receiving stavudine (Kumarasamy et al, 2003; Forna et al, 2007; Laurent et al, 2007). One possible explanation for this difference is that these studies did not use low dose stavudine and recent studies have found a lower incidence of

peripheral neuropathy in patients on low dose stavudine compared to those on stavudine 40 mg.

Our findings also agree with those of Karara et al (2010) who reported the incidence rate of peripheral neuropathy to be 13 % with low dose stavudine compared to 23 % with a higher dose of 40 mg stavudine.

The median time to treatment change due to peripheral neuropathy and lipodystrophy in patients on stavudine was 12 months and 17 months respectively. This also agrees with a study conducted in India which found the median time before switching due to these ADRs to be 13 and 18 months respectively (Kumarasamy et al, 2003).

Another interesting finding in this study is that patients receiving zidovudine took a shorter time to switch regimens due to peripheral neuropathy and lipodystrophy compared to those receiving low dose stavudine (10vs 17months and 5 vs 12months). While the finding should however be interpreted with caution as it has not been evidenced in other studies, it should not be surprising as a systematic review on benefits and harms of antiretrovirals have not generally directly compared low dose stavudine and zidovudine.

In this cohort, majority of the patients (43.1 %) switched their first line regimen due to lipodystrophy. This finding has important implications especially given the frequency of ART modifications that have occurred in developed countries. There are also increasing reports of lipodystrophy related to NRTI use from cohorts in resource limited settings which mainly use zidovudine and stavudine (Pujari et al 2005; Griensven et al, 2006).

Table 2: Cox proportional hazard model for factors predictive of first regimen switch

Baseline characteristics	Bivariate analysis		Multivariate analysis	
	Crude HR (95 % CI)	P value	Adjusted HR (95 % CI)	P value
Treatment group: AZT+3TC+EFV/NVP	1.95 (1.32-2.87)	0.001	2.12 (1.38-3.26)	0.001
Age ≥ 40 years	1.04 (0.72-1.47)	0.825	1.03 (0.71-1.50)	0.868
Gender (Males)	1.08 (0.74-1.58)	0.679	1.01 (0.66-1.55)	0.959
Weight at ART Initiation	1.11 (0.79-1.57)	0.551	1.10 (0.75-1.60)	0.637
Baseline CD4 count < 100	0.92 (0.64-1.32)	0.663	0.98 (0.66-1.45)	0.922
Anaemia: Hb < 11	1.27 (0.85-1.90)	0.236	1.10 (0.71-1.72)	0.664
Presence of OI at Initiation	1.94 (0.90-4.20)	0.091	1.33 (0.45-3.87)	0.606
Co-morbidities (Renal, Diabetes, Hypertension, Hepatitis B)	1.15 (0.47-2.82)	0.756	1.01 (0.38-2.68)	0.978
WHO Stage IV	1.47 (0.87-2.49)	0.149	1.45 (0.71-2.99)	0.312
Alcohol consumption	0.72 (0.18-2.92)	0.646	1.03 (0.25-4.36)	0.963
Isoniazid use	1.73 (1.02-2.96)	0.043	1.69 (0.95-3.00)	0.074

Like several other studies have shown, anaemia was the main adverse effect resulting in switching of regimens in patients on zidovudine (33.3 %) and the median time to switching was 4 months (Carr and Amin, 2009).

In terms of efficacy outcomes, patients receiving stavudine were found to have a higher increase in CD4 counts at months 6, 12, 18 and 24. However this immunological efficacy did not differ significantly in patients receiving either stavudine or zidovudine based HAART. This agrees with a meta-analysis of six studies comparing zidovudine and stavudine in triple therapy regimens (Moyle G et al, 2004).

Interestingly, despite a concern for potentially worsening anaemia in patients on zidovudine, this study found the opposite to occur in those patients who did not switch their initial regimen. The study observed a sustained overall rise in haemoglobin levels in patients on both regimens with the rise being significantly higher in patients on zidovudine compared to those on stavudine. This finding is similar to that reported by a study in South Africa but contrasts with studies conducted in high-income countries. A meta-analysis of six clinical trials conducted in high-income settings identified a decline in haemoglobin, 0.4 g/dl at 6 months and 0.2 g/dl at 12 months after the initiation of a regimen containing zidovudine but not stavudine (Moyle et al, 2004). The difference between this study's observations and reports from high-income country cohorts may reflect more advanced HIV disease, malnutrition and higher levels of concomitant disease in our population.

The limitations in this study include the absence of viral load data, a superior indicator for ART efficacy than immunologic or clinical indicators. Viral load is not routinely monitored at KNH, and it is recommended that treatment centres such as KNH incorporate viral load testing in its HIV/AIDS management programme. As patients with low haemoglobin levels at ART initiation were less likely to be put on AZT treatment, the degree of anemia is likely to be a confounding factor responsible for some of the differences in haemoglobin levels observed in the two treatment arms.

5. Conclusion

This study has showed that patients initiated on a zidovudine based regimen were more likely to change their treatment compared to those on a low dose stavudine based regimens. The incidence rate of regimen switch was moderate in both the patients initiated on low dose stavudine and zidovudine but slightly higher in those treated with zidovudine.

The results of the study thus shows that AZT and d4T have comparable benefits, and puts into question whether d4T should be completely abandoned, when AZT with a comparable adverse outcomes still finds use.

Conflict of Interest declaration

The authors declare no conflict of interest

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