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Virological Response Following Anti-Retroviral Therapy Employing Once-A-Day 30 mg of Stavudine in HIV-Infected Patients: A 24-Week Randomized Controlled Study in Dar Es Salaam, Tanzania

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Background

Stavudine at a dose of 30mg has been in use for more Thana decade. Its toxicity remains a challenge and phase out has picked up. However, the information about viral load suppression (VLS) at once-a-day dosing is lacking. A prospective open-label randomized controlled study was conducted.

Methods: Naïve HIV infected patients were equally randomized either to receive stavudine 30mg once-daily or zidovudine standard dose regimens. Viral load, hemoglobin (Hb), alanine amino transferase (ALT), Body Mass Index (BMI), opportunistic infections (OIs) at baseline and six months were determined. Changes at baseline and six months were compared within and between-groups. Our outcome was the proportion of patients who attained VLS< 400 copies/mL at six months.

Results: Four hundred and eighty three patients aged ≥ 18 years were analyzed. The overall mean standard deviation (SD) age was of 39 (9) years, 41 (9) and 38 (9) for males and females respectively. The two groups were similar in demographic, clinical and other laboratory indices at baseline. At six months, VLS< 400 copies/mL was 73.2%, there was no statistically significant differences been groups. There was no statistically significant differences been males and females. Patients with age >40 years were more likely to have VLS by 8% compared to young ones, risk ratio (95% CI) being 0.921 (0.829, 1.023; p=0.1275)

Conclusion: Viral load suppression for stavudine 30 mg once-a-day was similar to zidovudine standard regimen. However, long follow up period is recommended to determine efficacy and long term side effects at our recommended dose.

Keywords: Virological response; Once-a-day 30 mg stavudine; HIV-infected patients

Introduction

Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) has been a global challenge especially in the sub-Saharan African countries since its discovery more than three decades ago.

Efforts have been made since the discovery of the first antiretroviral drugs that treats HIV infection in early1990s, stavudine was among of them. Stavudine based combination therapies have been in use for treatment of HIV-infection for more than 15 years, since its approval by Food and Drug Administration (FDA) [1].The active molecule of stavudine works intracellularly. Before stavudine is changed to active molecule, it is phosphorylated by intracellular thymidine kinase to stavudine 5'-monophosphate, which is then phosphorylated by thymidylate kinase to the diphosphate followed by nucleoside diphosphate kinase to stavudine 5'-triphosphate. Stavudine 5'-triphosphate terminates the elongation of proviral DNA because it is incorporated by reverse transcriptase into nascent DNA but lacks a 3'-hydroxyl group. Stavudine is most potent in activated cells probably because thymidine kinase is an S-phase-specific enzyme [2]. Stavudine has lower plasma half-life, however its mode of action and cellular half-life allow its once daily use [3,4].

Stavudine (d4T) has been widely used as part of highly active antiretroviral therapy (HAART) with great efficacy. Studies have indicated that stavudine has as good viral load suppression as other antiretroviral medicines even at a lower doses [3,5-7]. Despite being highly effective, use of stavudine based regimens has been eliminated from developed countries because of high rates of adverse events. At its original higher doses of 40 mg and 30 mg twice-daily side effects were more evident at 30 mg twice-daily. This resulted into a recommendation by WHO to use stavudine 30 mg twice daily regardless of patients' weight. Some years later, stavudine containing regimens were discovered to have great associated with metabolic complications, such as dyslipidemias, lipodystrophy and other mitochondrial toxicities, notably peripheral neuropathy and lactic acidosis. This led the World Health Organization (WHO) to recommend a phase out of stavudine containing regimens in all member states in 2009 [8]. Although WHO has recommended phase out of stavudine based regimen, implementation proved difficult in some countries. This was notably due to economic crisis, dwindled support for HIV/AIDS program from developed countries. To address the challenges of side effects related to stavudine use, studies were conducted to show its performance at low dose. A study conducted by Mc Comsey et al. 2008 recommended reduction of daily doses in order to reduce stavudine related side effects, this study also retained the twice daily dosing [8,9].

Our study investigated the viral load suppression effect by stavudine (30 mg at aonce-a-daydosingin combination with other antiretroviral drugs). The main reason was to maintain stavudine as part of treatment regimens in the developing countries while reducing its associated side effects.

Materials and Methods

Registration Number of the Study: PACTR201208000402280

Study design

This was an open-label, randomized, and controlled study, in which the clinicians, pharmacist and the patients were aware of the study regimens. However, allocation of patients to a certain study group was randomly generated by randomization software as developed by Saghaei 2004 [10].

Study settings and population

HIV-infected subjects (age ≥ 18 years) were recruited from Care and Treatment Clinics (CTC) in Dar es Salaam city. The CTCs in Dar es Salaam are partly supported by Management and Development for Health (MDH) program that receives support from Presidential Emergency Program for AIDS Relief (PEPFAR). Apart from support from MDH the clinics are situated at government facilities and additionally receive contribution from the government. Our study was conducted in four of the many CTCs in Dar es Salaam which are Mwananyamala, Temeke, Amana hospitals and at Infectious Disease clinic (IDC). Selection of the study sites was based on the high enrolment and antiretroviral therapy initiation rates of eligible HIV infected patients.

Inclusion criteria required patients who were HIV-infected as confirmed by positive HIV antibody test, patients who were able to give informed consent, eligible for initiation of antiretroviral therapy and naïve to antiretroviral medicines as determined by self-reporting. Exclusion criteria included pregnant women and women who indicated intention to become pregnant during the study period as determined during initial assessment, a history of mental disorder, clinically diagnosed peripheral neuropathy and lipodystrophy.

Sample Size and study procedures

Five hundred and twenty subjects were randomized equally to group one and group two according to group randomization software method established by Saghaei 2004 [10]. The sample size was calculated based on 90% power, at significance level of 5%, assuming no differences in viral load suppression between the two groups in a two-sided study. Patients in group one received standard regimen that contained AZT at 300 mg, lamivudine 150 mg given twice daily and efavirenz at 600 mg while those in group two received a modified regimen that contained Stavudine 30 mg, lamivudine 300 mg and efavirenz 600 mg all given as once-a-daily doses [11]. The study drugs were provided free of charge by the Government through the Medical Stores Department (MSD). Patients visited the clinic on a monthly basis with the total follow up period of six months. Patients were asked to remain on the assigned medication until when these were changed by the study clinician based on presence of untoward effects.

Clinical assessment

Recruitment of patients started on November 7th, 2011. Patients were followed up for six months. At enrolment demographic information and anthropometric data were recorded. At baseline and at six months clinical assessments were conducted and recorded in the case report form (CRF). We diagnosed lipodystrophy by use of standardized case definition-based questionnaire and clinical assessment at baseline and six months. This instrument has been validated in African settings and is a combination of patient self-assessment and inspection by the clinician of body areas (face, neck, chest, abdomen, arms, legs and buttocks). Body shape changes were scored as absence, mild, moderate or severe [9,12] .

Laboratory procedures

Viral load was measured at baseline and six months by COBAS Ampli Prep/COBAS Taq Man HIV-1 Test, version 2.0 (Roche, Switzerland). Hemoglobin was measured at baseline and at six months by Penta 80 (ABX Penta 80 serial number 602P802149, France). Liver function was determined by serum alanine aminotransferase (ALT) determined at similar intervals by Cobas Integra 400 Plus (Roche Diagnostic Ltd SN399096 Rotkreuz, Switzerland).

Study end-points

The primary outcome was viral load suppression to less than 400 copies/mL at six months.

Statistical methods

Data were double entered into a secure Microsoft Access database. All analyses were performed using Stata (version IC/12.1; 4905; Stata corp; College Station, Texas 77845 USA). Patients' baseline characteristics were compared using Chi-squared and t-tests for categorical and continuous variables respectively. Between study groups comparison of viral load, was performed using student t-test. We used paired t-test to compare within the groups categories at baseline and at six months. All tests were two sided at 5% level of significance. Logistic regression was performed to determine factors determining VL Samong the following factors; group, age, sex, Liver enzyme (serum alanine aminotransferase [ALT]), body mass index (BMI) and WHO stage.

Viral load suppression was defined as presence of HIV-1 RNA particles of less than 400 copies/mL at six months of follow up. Age groups were classified as below 40 years and ≥ 40 years. Hemoglobin content was classified as anemia if it was less than 12 g/dl and 13 g/dl for females and males respectively. Nutritional status was categorized based on the BMI as Underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) or obese (≥ 30 kg/m^2).

Ethical issues

The Institutional Review Board (IRB) of Muhimbili University of Health and Allied Sciences (MUHAS) approved the study. Permission was granted by the respective Municipal authorities where the facility resided. The study was registered by the Pan African Clinical Trial Registry (PACTR) with the registration number PACTR201208000402280. Patients provided written informed consent prior to enrollment.

Results

Patient characteristics

A total of 483(92.9%) of randomized patients were included in the analysis (Figure 1), of whom males were 149 (30.9%). The overall mean (SD) age was 39 (9) years, while it was 41 (9) and 38 (9) years for males and females respectively. There was no reported death or loss to follow up at six months.

Clinical and laboratory features at baseline

The baseline characteristics of patients are presented in (Table 1). Of note is the fact that majority of the patients (58.5%) had advanced disease (WHO clinical stage 3/4) at the start of antiretroviral therapy. There were no statistically significant differences between the study regimens in terms of indicated parameters, including the median (inter quartile range, [IQR]) Viral load which was 64713 (63377, 65341) and 65613 (64648, 147098) copies/ml in the stavudine and zidovudine arms respectively.

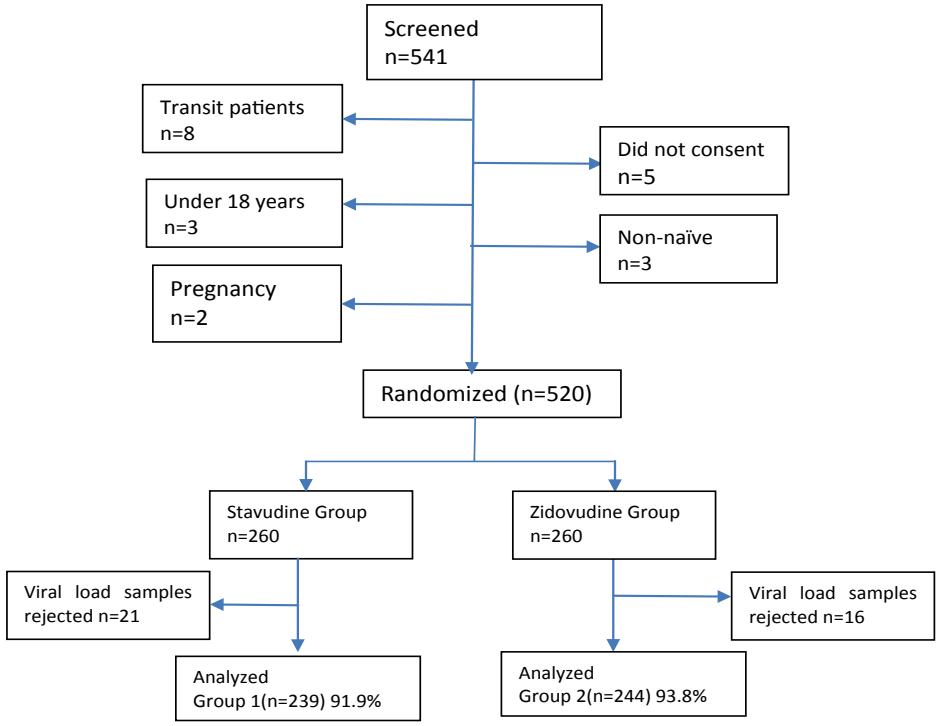

Figure 1: Study Patients Flow

Parameter		Stavudine n=239	Zidovudine n=244	p-value
Sex :	Male n (%)	76 (31.8)	73 (29.9)	
	Female n(%)	163(68.2)	171 (70.1)	0.6540
Age (year)	Mean± SD	38.9 ± 8.9	39.4 ± 9.0	0.5265
Age group n (%) year	≤ 40	153 (64.0)	139(57.0)	
	>40	86 (36.0)	105 (43.0)	0.1130
Body mass Index (kg/m2)	Mean ± SD	21.7 ± 2.7	21.6 ± 2.7	0.4195
	Underweight	31(13.0)	35 (14.3)	
	Normal	183(76.6)	174(71.3)	
	Overweight	25(10.5)	35(14.3)	0.3530
WHO Stage n (%)	Stage 1	20 (8.4)	21 (8.6)	
	Stage 2	83 (34.7)	74 (30.3)	
	Stage 3/4	136 (56.9)	149 (61.1)	0.5820
Hemoglobin (mg/dl)	Mean ± SD	9.4 ± 1.6	9.2 ± 1.7	0.1939
	Normal	18 (7.5)	17 (7.0)	
	Anemia	221 (92.5)	227 (93.0)	0.8110
Alanine aminotransferase (U/L)	Mean ± SD	17.1 ± 12.3	16.9 ± 13.7	0.8661
Viral Load (copies/mL)	Log10VL ± SD	4.896 ± 0.229	4.863 ± 0.168	0.0682

Table 1: Baseline characteristics of study patients

Characteristics during follow up

At six months of follow up, about 73.2% of patients attained viral load suppression of less than 400 copies/mL. When patients were compared by groups, there were no statistically significant differences between stavudine (30 mg once-a-day) and zidovudine based regimens in terms of virological suppression, p= 0.296. Although there was no statistically significant between males and females in terms of viral load suppression in the study groups, stratification by group and gender indicated that males in the stavudine group had 21% more compared to zidovudine group to have virological suppression, risk ratio (95% CI) being 0.79 (0.45, 1.39; p=0.4181). On the other hand results showed that females in the stavudine group had 56% more compared to those on zidovudine group in terms of virological suppression, risk ratio (95% CI) being 0.44 (0.29, 0.74; p=0.0009). There was no statistically significant differences between females and males in terms of viral load suppression, risk ratio (95% CI) being 0.93 (0.66, 1.32; p=0.6748) based on the baseline WHO stage Stratification of study group, age and viral load suppression indicated

that, patients with age below 40 years on zidovuine group were more likely to have viral load suppression compared to patients on stavudine group risk ratio (95% CI) being 0.58 (0.34, 0.98; p=0.0342). When patients were categorized in terms of Hemoglobin level, about 361 (74.7%) of 483 patients were anemic. When patients with anemia were stratified by study group and viral load suppression, patients on stavudine group were similar to those in zidovudine group in terms viral load suppression, risk ratio (95% CI) being 0.90 (0.65, 1.25; p=0.5329).

There were no statistically significant differences between baseline WHO stage and virological failure. Stratification by study group and WHO stage showed that, patients on stavudine group with WHO stage 3 or 4 were 25% less likely to have virological failure compared to those on zidovudine group risk ratio (95% CI) being 0.75 (0.54, 1.04; p=0.0750).

Overall there was a statistically significant decrease in reported opportunistic infections in groups between baseline and six months, p<0001. However, there was no statistically significant difference between groups in terms of baseline WHO stage. On the other hand, opportunistic infections were 40% less likely to develop in stavudine group compared to zidovudine group for patients with viral load ≥ 400 copies/mL, risk ratio (95% CI) being 0.60 (0.60, 6.43; p=0.0667).

Very few cases of drug related adverse effects were reported, in total there were nine cases of mild numbness on upper extremities, one from stavudine group and eight from zidovudine group and there was no any reported case of lipodystrophy at six months.

About 318 (65.8%) of patients had normal weight at six months, and there was statistically significant increase of BMI compared to baseline, p<0.0001. At six months of follow up results showed no statistically significant difference between the study groups in terms of BMI, p=0.360.. At six months of follow up, 14(2.9%), 318 (65.9%), 134 (27.7%) and 17 (3.5%) were underweight, normal, overweight and obese respectively. Underweight patients on stavudine group were similar to patients on zidovudine group to develop virological failure, risk ratio (95% CI) being 0.57 (0.14, 2.36; p=0.4285). But patients on stavudine group with normal weight were 23% less likely to develop virological failure compared to zidovudine group, risk ratio (95% CI) being 0.77 (0.54, 1.11; p=0.1583 (Table 2).

Discussion

Stavudine based regimens have been weaned off in the treatment of HIV/AIDS in many countries although complete phase out has not been successful in the developing countries. Our study has been looking into the possibility of stavudine to be resumed as part of an alternative drug in HIV treatment when the current best options have not role. According to our knowledge, this is the first randomized study to investigate the use of once daily stavudine30mg in combination with other antiretroviral drugs to assess its performance in terms of viral load suppression and immunological recovery among naive HIV infected patients.

Our study recruited subjects from patients who could decide to have health services for their choice. The findings indicated that, compared to females, males started treatment for HIV infection at an advanced stage of WHO stage 3 or 4. Since in most of the societies males are less likely to attend medical attention until are seriously sick, it is probably the case even in the treatment of HIV [13]. On the other hand, women start treatment early probably due to their responsibility in taking care of children including taking them to hospitals [14-16]. Hospitals have provider initiated counseling and testing programs including prevention of mother-to-child transmission (PMTCT) [17], these are entry points for them to know their sero status and have medical attention earlier than men [15,18].

Human immunodeficiency virus (HIV) causes substantial decline in CD4+ T cell counts if it remains unchecked. In our study the overall viral load suppression was statistically significant higher compared to baselines viral. Our finding indicated no statistical differences between groups. This was a promising finding due to the fact that stavudine 30 mg given once-a-day performed similar to the standard zidovudine based regimens. This is probably due to the facts that, antiretroviral drugs (ARVs) particularly nucleoside reverse transcriptase inhibitors work properly inside the cells. This was depicted by the fact that, even though the plasma concentration is low, intracellular concentrations suffice to inhibit viral replications. Our findings are comparable to the findings reported by Hoffmann (2009), the results indicated that viral load suppression at six months for stavudine 30 mg (twice-a- day) in combination with other drugs was 79% [19].

We did not find statistically significant gender differences in terms of viral load suppression [20]; however females had higher virological failure compared to men in both study groups. The reason behind this might probably be due to lack of disclosure of HIV status by females. As a result medicines are taken inconsistently, lack of support from male partners and family members or overwhelmed with family activities including taking care of children [21].A study conducted by Cescon reported similar findings when evaluating time to virological suppression in which among factors associated with the outcome was male sex [22]. A literature review on adherence to antiretroviral therapy (ART) in developed countries revealed that thirty of the 44 articles (68.2%) that reported comparative data on adherence by gender found women to be less adherent than men [23].

In our study we did not find statistically significant differences between stavudine and zidovudine in terms of opportunistic infections after starting antiretroviral drugs. However, we found statistically significant decrease in the occurrence of opportunistic infections from baseline to six months in both groups. This was probably due the fact that, patients on ARVs have declining viral load with an improved immune system that fights against opportunistic as well as external germs. This was consistent with other studies that report decrease of opportunistic infections for patients who started antiretroviral therapy (ART) [24,25].

ART is associated with the occurrence of side effects, our study indicates nine cases of mild numbness and most of them were on zidovudine group.

Parameter		Stavudine (d4T) (n=239)			Zidovudine (AZT) (n=244)			At Six months d4T vs AZT
		Baseline	Six Months	p-value	Baseline	Six Months	p-value	P value
Body mass Index (kg/m2)	Mean ± SD	21.7 ± 2.7	23.7 ± 3.3	<0.0001	21.6 ± 2.7	23.3 ± 3.2	<0.0001	0.174
Hemoglobin (mg/dl)	Mean ± SD	9.4 ± 1.7	10.8 ± 1.9	<0.0001	9.2 ± 1.7	10.3 ± 2.2	<0.0001	0.003
Alanine aminotransferase (U/L)		17.1 ± 12.3	24.5 ± 18.4	0.0003	16.9 ± 13.7	24.8 ± 17.1	<0.0001	0.872
CD4+T cell (cell/mm3) recovery			116±84			108 ± 93		0.408
Viral Load (log10VL)		4.896 ± 0.229	2.325 ± 1.419	<0.0001	4.863 ± 0.168	2.334 ± 1.203	<0.0001	0.945
Viral Load (copies/mL)	<400		178 (76.1)			173 (70.9)		0.201
	≥ 400		56 (23.9)			71 (29.1)		

Table 2: Comparison within study groups at baseline and six months and between groups at six months of follow up for patients

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Fewer cases that were reported on stavudine group were probably due to low dose of stavudine. Similar findings were reported by Mc Comsey and Cournil, who noted significantly fewer side effects for the patients who used stavudine at low compared to high doses [9,26]. Among of the disgusting side effects for patients on ART, particularly stavudine based regimens are lipodystrophy, we could not find any reported cases for lipodystrophy in our study. Lipodystrophy is associated with long term use of stavudine [27]; low dose of stavudine partly might explain the absence of this condition in our study.

Nutrition is one of the components in the success of ART. In terms of BMI, our study had many patients with normal BMI at six months and it was significant increase compared to baseline in both groups. This indicated that, patients on ART have few illnesses that might hinder their feeding behavior and absorbability of nutrients in the gut [28]. Our findings indicated few patients were underweight at six months. The probable cause for this might be due to most patients resume their normal feeding behavior as their health gets improved. Therefore the remained few patients with low BMI were probably due to poor adherence to ART, which cause rebounded viral replication hence occurrence of OIs which affects their nutrition status [29]. On the other hand patients who recover from illness tend to eat frequently for compensation of energy and protein loss due to illness. This causes some of them to have BMI above normal. Study conducted by Lakey showed similar trends for patients who started combination ART in which there was significant increase in BMI from 26.4 to 27.9 kg/m^2, $p<0.0001$ [30].

Our findings indicated stavudine 30 mg given once-a-day in combination with other antiretroviral drugs had promising results and was comparable with the current drugs. This implies that stavudine 30 mg can substitute other drugs in the event they produce intolerable side effects for drugs like tenofovir, zidovudine and abacavir. Early onset of side effects related to zidovudine, abacavir and tenofovir can be alleviated by initiating stavudine 30 mg once-a-day. This can give time for patients to acclimatize on the ART with the ultimate improvement of adherence. Initiating patients with stavudine 30 mg provides reserve for many drug options in future; patients can remain in the first line regimens for long period in life time before switched to second line regimens. Second line regimens are costly and are associated with more side effects compared to first line regimens. Our findings did not find many stavudine related side effects probably due to short follow up period, therefore a long follow up study is recommended to reveal its performance.

In conclusion, stavudine 30 mg once-a-day has similar viral load suppression compared to zidovudine. Stavudine based regimens have the roles to play in the resource constrained countries, phase out should be reconsidered especially for patients that cannot tolerate tenofovir, zidovudine andabacavir.

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Conflicts of Interest

There were no potential conflicts of interest disclosed.

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