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COMPARISION OF EFFICACY OF STAVUDINE AND ZIDOVUDINE ON CD4 COUNTS IN TRIPLE DRUG THERAPY REGIMEN IN PATIENTS WITH HIV INFECTION - A RETROSPECTIVE STUDY

Kiran LJ*, Gokul CG, Santhosh Ramakrishna, Narendranath S
Department of Pharmacology, J. J. M. Medical College, Davangere, Karnataka, India

***Corresponding Author:** Dr. Kiran LJ, Assistant Professor, Department of Pharmacology, J. J. M. Medical College Davangere, Karnataka, India

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Abstract: The main objective of the study is **1.** To compare the effect of triple drug therapy with stavudine + lamivudine + nevirapine on CD4 counts 6months and 12 months after therapy. 2. To compare the effect of triple drug therapy with zidovudine + lamivudine + nevirapine on CD4 counts 6months and 12 months after therapy. 3. To compare the efficacy of the above two mentioned regimens. **Methods:** In this retrospective study, data was collected from the antiretroviral therapy (ART) Centre where 46 subjects infected with HIV received stavudine + lamivudine + nevirapine and 54 subjects infected with HIV received zidovudine + lamivudine + nevirapine. Baseline CD4 counts were recorded and compared with CD4 counts after 6 months and 12 months after therapy in each regimen. Changes in CD4 counts in both the regimen were also compared. Statistical analysis was done using ANOVA followed by Tukey test for group wise comparison. **Results:** Statistical analysis showed that there was no significant change in CD4 count after 6 months of treatment in stavudine group whereas there was significant increase in CD4 counts after 12 months after therapy with stavudine + lamivudine + nevirapine. But there was a significant increase in CD4 counts after both 6 months and 12 months of treatment with zidovudine + lamivudine + nevirapine. But when efficacy of both the regimen was compared with each other there was no significant change in the CD4 counts. **Conclusion:** This nevirapine and zidovudine + lamivudine + nevirapine are equally efficacious but improvement of CD4 counts after initial 6 months of therapy is better with zidovudine + lamivudine + nevirapine treated group than compared with stavudine + lamivudine + nevirapine treated group.

Key words: HIV, Zidovudine, Stavudine, Lamivudine, Nevirapine, CD4 Count.

INTRODUCTION

AIDS has grown to pandemic proportions resulting in 25 million deaths and 40 million persons living with human immunodeficiency virus (HIV) worldwide by the end of 2005[1] With 3.7 million human immunodeficiency virus (HIV) positive in India, many predict that this nation of 1 billion people will soon see infection rates soar if successful prevention programs are not implemented. Although the Government of India has designed various programs to help prevent the further spread of HIV, lack of funding and poor regulatory systems are further barriers to their implementation. India's AIDS control strategy must design successful programs to prevent infection rates from multiplying rapidly [2].

Clinical advances have been supported by increased understanding of virologic and immunologic markers of disease stage, viral transmission, and the evolution of viral resistance to antiretroviral drugs. These advances coincided with major breakthroughs in the understanding of disease pathogenesis, the introduction of viral load monitoring and the clinical application of drug resistance testing [3, 4, 5, 6].

Antiretroviral therapy is recommended for all patients with symptomatic HIV disease [7]. For patients without symptoms, therapy should be initiated at some point after the CD4 cell count declines below350/µL but before it reaches 200/µL. No new evidence has emerged to define the optimal CD4 cell count that provides a treatment-related survival advantage, and based on the inherent difficulty with designing and executing such studies, it is unlikely that a randomized, controlled trial will be conducted to answer this question. Rather, recommendations rely on well conducted cohort studies[8]. Data from one observational study showed a benefit to starting therapy when CD4 cell counts were higher than 350cells/µL compared with starting at an unspecified later time, but these data do not resolve the questions of the precise CD4cell count at which to start [9].

The recommended initial regimen remains a combination of 2 nRTIs with either an NNRTI or a PI boosted with low-dose ritonavir. Although the majority of HIV infected people in need of antiretroviral therapy are not yet receiving treatment, a considerable number of patients (1.3million) were receiving highly active antiretroviral therapy (HAART) in resource poor settings by the end of 2005[10]. Most first line HAART regimens for adults in resource poor settings include a nucleoside reverse transcriptase inhibitor (NRTI)

backbone of either stavudine (d4T 40 mg twice daily) or zidovudine (AZT 300 mg twice daily) in combination with lamivudine (3TC 150 mg twice daily). Stavudine plus lamivudine is commonly used as it is available in a generic combined formulation with nevirapine. Published data from a number of HIV cohorts have shown that HAART is effective in resource poor settings[11]. At the same time, as new antiretroviral drugs become available, clinicians in resource rich settings are prescribing combinations including stavudine or zidovudine less frequently[12].

Stavudine the thymidine analog stavudine (d4T) has high oral bioavailability (86%) that is not food-dependent. The major dose-limiting toxicity is a dose-related peripheral sensory neuropathy. The incidence of neuropathy may be increased when stavudine is administered with other neuropathy-inducing drugs such as didanosine and zalcitabine, or in patients with advanced immunosuppression. Symptoms typically resolve completely upon discontinuation of stavudine; in such cases, a reduced dosage may be cautiously restarted. Lactic acidosis with hepatic steatosis, as well as lipoatrophy, appears to occur more frequently in patients receiving stavudine than in those receiving other NRTI agents[13].

Zidovudine (azidothymidine; AZT) is a deoxythymidine analog was the first antiretroviral agent to be approved and has been well studied. The drug has been shown to decrease the rate of clinical disease progression and prolong survival in HIV-infected individuals. The most common adverse effects of zidovudine include myelosuppression, macrocytic anemia (1-4%) or neutropenia (2-8%). Extreme fat loss may be more common than with other agents [13].

In this present study efforts are made to compare the effect of stavudine and zidovudine triple drug therapy regimens on CD4 count in patients with HIV infection.

MATERIALS AND METHODS

Objectives:

I. To compare the effect of triple drug therapy with stavudine + lamivudine + nevirapine on CD4 counts 6months and 12 months after therapy.
II. To compare the effect of triple drug therapy with zidovudine + lamivudine + nevirapine on CD4 counts 6months and 12 months after therapy.
III. To compare the efficacy of the above two mentioned regimens.

Study design:

This is a retrospective study; data is collected from the antiretroviral (ART) center in a private hospital and medical college. The patients were grouped based on the two regimens stavudine + lamivudine + nevirapine and zidovudine + lamivudine + nevirapine. The data regarding CD4 counts were collected randomly from the case forms in ART center from the period of June 2009 to June 2011.

Methodology:

In this study data regarding the CD4 count were collected from 100 case forms (patients who are on triple drug regimen for AIDS) from the period of June 2009 to June 2011. Out of which 46 patients infected with HIV were receiving stavudine (40mg) + lamivudine (150mg) + nevirapine (200mg) and 54 subjects receiving zidovudine (300mg) + lamivudine (150mg) + nevirapine (200mg) triple drug therapy. Both the drug regimens were prescribed twice a day and 7 days a week. Patients were asked to come for follow up after every month along with empty strips of medication to check for adherence. Baseline CD4 counts were recorded before the initiation of ART which was compared with CD4 counts after 6 months and 12 months of therapy in each regimen. All patients provided written informed consent data was collected after institutional ethics committee has given clearance for the study.

The patients age less than 20 years and more than 60years, severely immune-compromised, opportunistic infection except TB (candida, STD, cytomegalovirus), patients taking regimens other than above mentioned ones, and anemic patients were excluded from this study.

Statistical analysis:

Results are presented as Mean ± SEM. One way ANOVA was used for multiple comparisons followed by Tukey's post hoc test for comparison between groups. For all the tests a 'P' value of 0.05 or less was considered for statistical significance. Graph pad prism version 5 statistical software was used for the analysis.

RESULTS

Totally 100 patients case forms were analyzed randomly out of which 56 were receiving stavudine regimen and 46 were receiving zidovudine regimen. Mean age of patients in stavudine group is 33.30±11.75, among these 15 males and 31 were females. Mean age in zidovudine group is 34.57±43.33 out of these 19 males and 35 were females (Table.1 & Figure.1).

Table.1: Demographic data

Groups	Mean age	Age range	Male	Female	Tuberculosis
Stavudine regimen	33.30±11.75	22-56 years	15	31	2 Cat-2, 7 past history
Zidovudine regimen	34.57±43.33	25-50 years	19	35	4 Cat-1, 9 past history

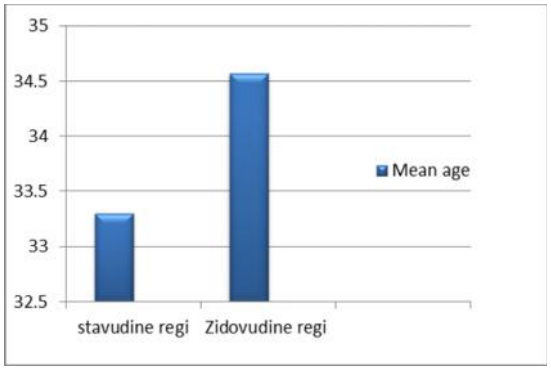

Figure.1: Bar graph showing age distribution of two groups

In this study, CD4 count in zidovudine baseline 263±205, after 6months 410±192 (p<0.05) and after 1year of ART therapy 484±380 (p<0.0001). CD4 count in stavudine group 284.5±231, at 6 months 388±268 (p > 0.05) and after 1 year of ART therapy CD4 count increased to 471±233 (p < 0.05) (Table.2). In zidovudine group the CD4 count start increasing after 1 year of ART therapy but in case of stavudine group CD4 count increased by 6 months. There was no statistically significant difference between the baseline CD4 counts of two regimens (Table.2, Table.3 & Figure.2).

Table.2: Showing Mean CD4 count between the two groups

Groups	CD4 count/ Mean ± SD	SE
Zidovudine Baseline	263±205	27.8
Zidovudine 1 visit (6 months)	410±192	26.2
Zidovudine 2 visit (12 months)	484±380	51.72
Stavudine Baseline	284.5±231	34.9
Stavudine 1 visit (6 months)	388±268	40.3
Stavudine 2 visit (12 months)	471±233	35.2

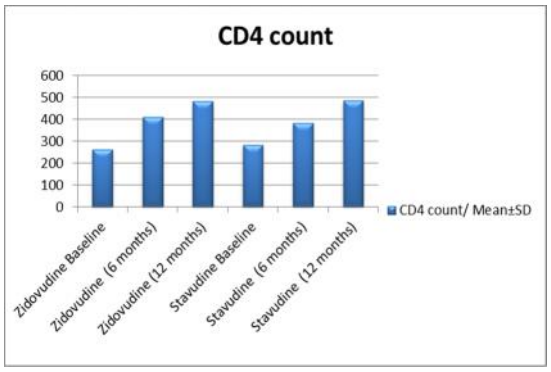

Figure.2: Bar graph showing CD4 count in two regimens at 6 months and 12 months.

DISCUSSION

In this present study attempt has been made to compare the effect of triple drug therapy with zidovudine + lamivudine + nevirapine and stavudine + lamivudine + nevirapine on CD4 counts 6months and 12 months after therapy. In this retrospective study randomly selected case forms of patients with AIDS who are on ART were observed for CD4 count at 6 months and 12 months after starting ART. From above results CD4 count in zidovudine baseline 263±205, after 6 months 410±192 (p <0.05) and after 1 year of ART therapy 484±380 (p<0.0001). CD4 count in stavudine group 2845±231, at 6 months 388±268 (p>0.05) and after 1 year of ART therapy CD4 count increased to 471±233 (p < 0.05). In stavudine group the CD4 count start increasing after 1 year of ART therapy but in case of zidovudine group CD4 count increased by 6 months. This study shows that both the treatment regimens namely stavudine + lamivudine + nevirapine and zidovudine + lamivudine + nevirapine are equally efficacious but improvement of cd4 counts but after initial 6 months of therapy is better response seen with zidovudine + lamivudine + nevirapine treated group than compared with stavudine + lamivudine + nevirapine treated group. Both regimens were well tolerated among both patients most common adverse effect in stavudine regimen is lipodystrophy and peripheral neuropathy and among zidovudine regimen anaemia is most commonly observed.

Table.3: Tuckey's multiple comparison test between groups

DIFFERENCE BETWEEN GROUPS		
GROUPS COMPARED	**MEAN DIFFERENCE**	**(P <0.05) significant/not significant**
Zidovudine baseline VS stavudine baseline	21.6	NS
Zidovudine Baseline vs Zidovudine 6 months	-147*	S
Zidovudine Baseline vs Zidovudine 12 months	-220.3***	S
Stavudine Baseline vs Stavudine 6 months	-104	NS
Stavudine Baseline vs Stavudine 12 months	-187*	S

S=significant, NS= not significant * p<0.05, *** p<0.0001

A study conducted by Moore et al, their analysis described a decline in opportunistic illness and death in a clinical cohort characterized by a high percentage of patients of minority race and a history of injecting drug use. This decline appears to be a result of the use of potent combination antiretroviral therapy and has affected most, but not all, illnesses. In patients receiving three-or-more drugs combination therapy, the CD4 level is probably the best immediate predictor of the risk of developing an opportunistic illness or of dying, with the HIV-1 RNA response a predictor of outcome in as much as it correlates with subsequent CD4 level. The concurrent CD4 level is probably the best correlate of development of opportunistic illness or death. As the duration of time on potent combination antiretroviral therapy increases further, it will continue to be important to assess the changing natural history of HIV disease and the effectiveness and

durability of current and new HIV therapies in clinical practice [14].

In patients with HIV infection, CD4 positive lymphocyte (CD4) count is a widely discussed candidate for a surrogate outcome for clinical AIDS and death. Unfortunately, the available data suggest that CD4 count is not reliable enough to serve as a valid surrogate outcome. AIDS, by the Centers for Disease Control (CDC) clinical criteria, could be considered a surrogate for death because of the severely compromised immune system that it implies. Other clinically valid measures of immune function such as P-24 antigen levels and plasma HIV viral load have been suggested as possible surrogate outcomes but are unproven [15].

In this present study only CD4 count was used as predictor of clinical progression and efficacy of ART triple therapy, the reason for decreased response in stavudine regimen is not known. The above mentioned study concluded CD4 count can used as predictor of disease progression. In this study results, zidovudine regimen showed significant improvement in the CD4 count at 6 months compared to stavudine regimen which showed improvement in CD4 count after 12 months of therapy. The reason for this response is not known. The resistance may not be the cause for this late response in stavudine group because virus which is resistant to zidovudine is also having cross resistance to stavudine[16].

CONCLUSION

From this we can conclude that zidovudine regimen patients had better prognosis compared to stavudine regimen. But combined measurements of plasma HIV RNA and CD4 cell counts being more accurate for determining the prognosis of HIV-seropositive patients on antiretroviral treatment[17].

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