Research Article

Comparing Efficacy and Safety of Stavudine Plus Lamivudine Versus Zidovudine Plus Lamivudine in Combination with Nevirapine in HIV Infected Individuals Receiving Antiretroviral Therapy in Rural Tertiary Care Teaching Hospital in Central India

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ABSTRACT

Main objective of study is to compare the safety and efficacy of Zidovudine (AZT) + Lamivudine (3TC) with Stavudine (d4T) + 3TC, each in combination with Nevirapine (NVP). It is a retrospective observational study conducted in the ART centre of a tertiary care teaching hospital in central India. Two hundred sixty three cases on antiretroviral therapy were studied retrospectively. One hundred twenty eight cases were on Stavudine based regimen and one hundred thirty five cases on Zidovudine based regimen. An active search was also done for adverse reactions and opportunistic infections. Statistical analysis was done using SPSS20 software. CD4 cell count measured at 6-8 months and 12-14 months of therapy. CD4 cell count increased significantly in both treatment groups. There was no statistically significant difference between the baseline CD4 counts of two regimens. Incidence of opportunistic infection were slight more with Zidovudine group (in 30.37% patients) compared with Stavudine group (in 27.34% patients). Out of 135 cases in AZT group, 39 had adverse drug reactions (ADRs); while 29 out of the 128 cases in d4T had adverse drug reactions. Zidovudine associated with early and mild ADRs while Stavudine associated with late and distressing ADRs. Both the regimens were equally efficacious. Stavudine related to late occurring, well recognised and more distressing toxicities so preference should be given to AZT-based regimen.

Keywords: Antiretroviral Therapy, AIDS, ADRs, HIV.

INTRODUCTION

HIV/AIDS remains one of the world's most significant public health challenges, particularly in low and middle income countries. HIV/AIDS is a global pandemic.[1] The introduction of highly active antiretroviral therapy (HAART) has led to a significant reduction in AIDS related morbidity and mortality.[2-4] Antiretroviral therapy (sometimes called Highly Active Antiretroviral Therapy or HAART) typically combines three or more antiretroviral drugs that work together to keep HIV from multiplying. First-line therapy should consist of an NNRTI + two NRTIs. Deciding which treatment regimen to begin for first-line treatment in ART-naïve patients, however, remains a significant challenge. Two of the most commonly used medications include Stavudine (d4T) and Zidovudine (AZT).

Stavudine (d4T) and Zidovudine (AZT) belong to nucleoside reverse transcriptase inhibitor (NRTI) group of drugs and they are the core drugs with Lamivudine (3TC) as the first-line therapy.

Unfortunately, up to 25% of patients discontinue their initial HAART regimen because of treatment failure (inability to suppress HIV viral replication to below the current limit of detection, 50 copies/μl), toxic effects or noncompliance within the first eight months of therapy.[5,6]

Continuous evaluation of the benefit and harm of ART will help to achieve the ultimate goal of making safer and more effective treatment available to patients. The purpose of this study was to assess which of these two medications was the best for initial treatment for people living with HIV.

MATERIALS AND METHODS

Objective

To compare the safety and efficacy of Zidovudine (AZT) + Lamivudine (3TC) with Stavudine (d4T) + 3TC, each in combination with Nevirapine (NVP) according to;

- Difference in CD4 count after six to eight months and after twelve to fourteen months of therapy
- Incidence of Opportunistic Infections
- Incidence of Adverse Drug Reactions

Study design

It is a retrospective observational study conducted in the Anti Retroviral Therapy (ART) centre of a tertiary care teaching hospital in central India.

Source population

The source population consist of AIDS patient on anti retroviral therapy. HIV-positive cases who were already on ART and who were newly started on ART were included. The patients were grouped based on the two regimens Stavudine + Lamivudine + Nevirapine and Zidovudine + Lamivudine + Nevirapine.

Methodology

Two hundred sixty three cases on antiretroviral treatment (ART) were studied retrospectively. One hundred twenty eight cases were on Stavudine based regimen, and one hundred thirty five cases were on Zidovudine based regimen.

Data about Adverse drug reactions (ADRs), opportunistic infections and CD4 count were collected from case records in ART center and an active search was also used to collect ADRs for the duration of one year.

Statistical analysis

Results are presented as Mean ± SEM. Paired T test and independent T test was used for comparing different outcomes with different regimens. Statistical analysis was done using SPSS20 computer software.

RESULTS

Baseline characteristics: Table 1 contains the baseline characteristics for patients by treatment group. In the d4T group out of 128 patients, 68(53%) were male and 60(47%) were female. Mean age of patients in group was 33.8±14.1 years and mean weight was 41.9±13.7kg. The mean CD4 T-lymphocyte count was 286.04±249.9.

In the AZT group out of 135 patients, 88(65%) were male and 47(35%) were female. Mean age of patients in group was 38.4±11.6 years and mean weight was 47.9±9.7kg. The mean CD4 T-lymphocyte count was 267±182.5. (Table 1)

Figure 1 shows age group wise comparison between patients on different regimens.

Table 1: Baseline characteristics

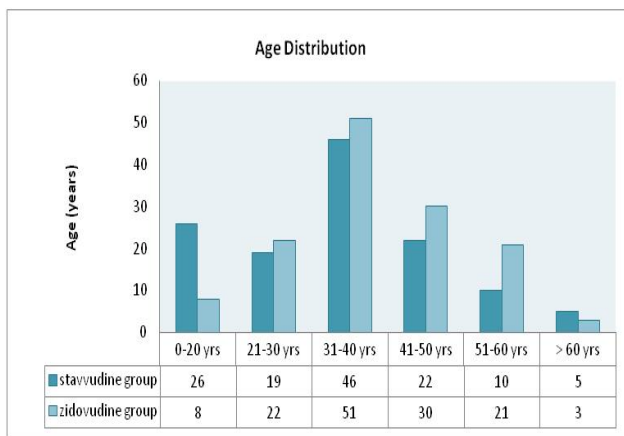| Groups	Male	Female	Age (years) Mean ± SD	weight (K.G.) Mean ± SD	CD4 cell count ($\times 10^6$ cells/liter) Mean ± SD
Stavudine regimen	68(53%)	60(47%)	33.8±14.1	41.9±13.7	286.0±249.9
Zidovudine regimen	88(65%)	47(35%)	38.4±11.6	47.9±9.7	267.0±182.5

Figure 1: Age distribution

Table 2: CD4 cell count

Treatment Groups	CD4 count ($\times 10^6$ cells/litre) Mean ± SD	Standard Error of mean
Stavudine CD4 Baseline	286.0±249.9	22.1
Stavudine CD4 after 6-8 months	364.3±238.7	21.1
Stavudine CD4 after 12-14 months	437.2±273.3	24.2
Zidovudine CD4 Baseline	267.0±182.5	15.7
Zidovudine CD4 after 6-8 months	354.3±188.7	16.2
Zidovudine CD4 after 12-14 months	402.9±204.2	17.6

Immunologic response to treatment

The CD4 cell count increased in both treatment groups (Table 2).

Baseline CD4 count in Stavudine group was 286.04±249.9, at 6-8 months 364.3±238.7 (p<0.05) and after 12-14 months of ART therapy CD4 count increased to 437.2±273.3 (p<0.05). In Zidovudine group mean baseline CD4 was 267±182.5, after 6-8 months of therapy 354.3±188.7 and after 12-14 months of therapy mean CD4 was 402.9±204.2. (Table 2/ Figure 2)

There was no statistically significant difference between the baseline CD4 counts of two regimens.
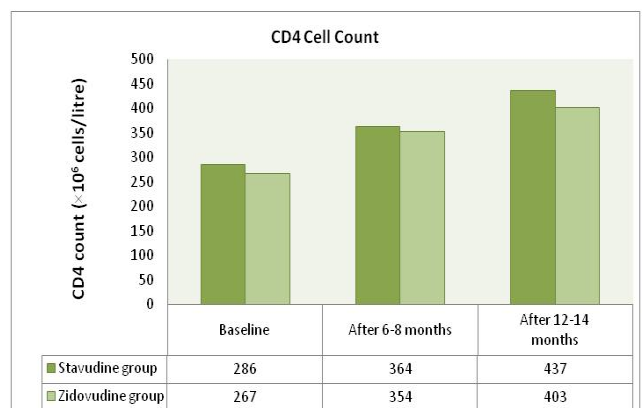

Figure 2: CD4 cell count

Comparing CD4 count after 6-8 months and after 12-14 months of therapy results were statistically significant (p<0.05) in same treatment group but when we compared result between two groups results were statistically insignificant. (Table 3)

Table 3: CD4 cell count comparison between groups

Group Compared	Mean Difference	(P <0.05) significant/not significant
Stavudine baseline versus Zidovudine baseline	-19.04	Not Significant
Stavudine Baseline vs. Stavudine 6 months	-78.23	Significant
Stavudine Baseline vs. Stavudine 12 months	-151.11	Significant
Zidovudine Baseline vs. Zidovudine 6 months	-87.3	Significant
Zidovudine Baseline vs. Zidovudine 12 months	-135.9	Significant

Figure 3: Opportunistic infections

Opportunistic infections

Common opportunistic infections were diarrhoea (38%),respiratory infection (34%), candidacies (22%) and herpes virus infection (4%).opportunistic infections were slight more with Zidovudine group (in 30.37% patients) compare with Stavudine group (in 27.34% patients).(Figure 3)
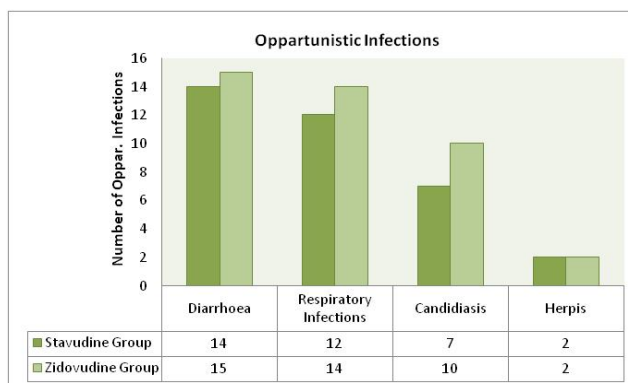
Adverse drug reactions profile

Out of 128 patients on Stavudine based regimen, 29 had total 45 ADRs; while 39 out of 135 patients on Zidovudine based regimen had total 72 ADRs. Peripheral neuropathy (24.4%) and Lipodystrophy (11.1%) were commonest ADRs due to Stavudine based regimen. ADRs related to gastrointestinal tract like nausea (19.4%) and vomiting (13.9%) were commonly presented ADRs in patients on Zidovudine based regimen. (Table 4/Figure 4)

Table 4: Types of ADRs

| Organ System	Types of ADRs	Stavudine group	Zidovudine group	Total Number
Gastrointestinal (GIT) 46 (39%)	Nausea	5	14	19
	Vomiting	2	10	12
	Abdominal pain	3	7	10
	Anorexia	3	2	5
Nervous system 25 (21%)	Peripheral Neuropathy	11	0	11
	Headache	1	8	9
	Dizziness/Vertigo	1	4	5
Musculo-skeletal 15 (13%)	Myalgia	0	8	8
	Arthralgia	1	3	4
	Weakness	2	1	3
Skin and appendages 11 (9%)	Skin Rashes	2	6	8
	Pruritus	0	1	1
	Pigmentation (nail)	1	1	2
Metabolic and nutritional disorders 9 (8%)	Lipodystrophy	5	0	5
	Weight Loss	4	0	4
Red blood cell disorders 1 (0.85%)	Anemia	0	1	1
Others 10 (9%)	Uneasiness	4	6	10
TOTAL		45	72	117
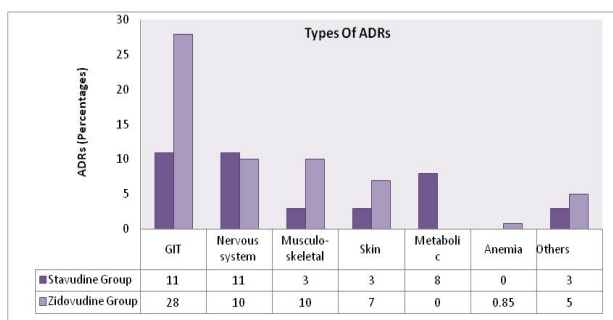
Figure 4: Types of ADRs
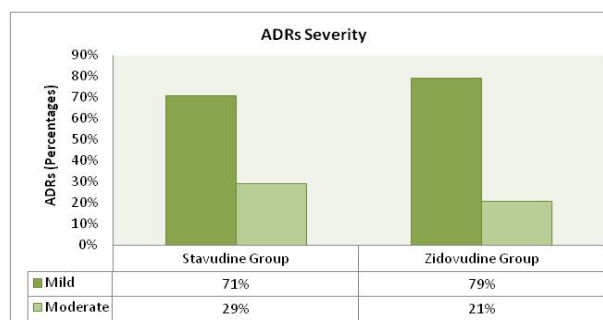
Figure 5: Severity of ADRs

Most of the ADRs were in mild category; 71% in Stavudine group and 79% in Zidovudine group.

DISCUSSION

This study compared the nucleoside analogue combinations Stavudine plus Lamivudine and Zidovudine plus Lamivudine when used in triple combination with Nevirapine. In this observational study randomly selected case forms of patients with AIDS who are on ART were observed for CD4 count at 6-8 months and 12-14 months after starting ART. An active search for patients with ADRs and opportunistic infections were also conducted for the duration of one year.

According to WHO recommendations - First-line therapy should consist of an NNRTI + two NRTIs, one of which should be Zidovudine (AZT) or Tenofovir (TDF). Countries should take steps to progressively reduce the use of Stavudine (d4T) in first-line regimens because of its well-recognized toxicities. Alternative options (AZT and TDF) are more expensive, require more laboratory monitoring and have higher initial discontinuation rates[7,8]. Cumulative exposure to d4T has the potential to cause disfiguring, painful and life threatening side-effects, such as lipodystrophy, peripheral neuropathy and lactic acidosis.[9]

Immunologic response to treatment and opportunistic infections

The baseline CD4 count and the trend of the CD4 response assessed by regular six monthly CD4 counts are needed to best characterize and define immunological failure. In most patients, CD4 cell counts rise with the initiation of therapy and immune recovery.

From the results of this study CD4 count significantly increased in both treatment groups after 6-8 months and after 12-14 months of therapy. This study shows that both the treatment regimens namely Stavudine + Lamivudine + Nevirapine and Zidovudine + Lamivudine + Nevirapine are equally efficacious. CD4 cell count elevations were pronounced in both the regimens, achieving statistical significance when analyzed as the time-weighted change from baseline.

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. Analysis of recent clinical trials indicates that both decreases in HIV-1 RNA plasma levels and increases in CD4 cell counts confer the most pronounced clinical benefit.[10]

Overall incidence of opportunistic infections in this study was 28.9%. Opportunistic infections were slight more with Zidovudine group (in 30.37% patients) compared with Stavudine group (in 27.34% patients). 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.

Adverse drug reactions profile

Limitations of antiretroviral therapies because of adverse events have been described and reported in literature. In this analysis a total of 117 adverse events have been reported by 68 patients that were studied. In Stavudine group, 29 patients had total 45 ADRs; while 39 patients on Zidovudine based regimen had total 72 ADRs.

Despite the lack of serious toxicity in our study, the frequent mild toxicities do influence a patient's willingness to adhere to a regimen. This may be especially pertinent for the patient who is treatment-naive and otherwise asymptomatic.

The incidence of ADRs was higher in patients with Zidovudine group then Stavudine group (29% vs. 23%), but more serious ADR were observed with d4T.

In this study, most commonly presented ADRs were related to GIT system (39%). Various studies show similar finding.[11-13] Gastrointestinal symptoms such as nausea, vomiting and abdominal pain occurred significantly more frequently in the Zidovudine group (28.2%). Other ADRs more frequently related to Zidovudine based regimen were myalgia (7%), headache (7%), rashes (5%) and arthralgia (3%).

Anaemia was also detected in one patient on Zidovudine based regimen. Most of ADRs related to Zidovudine were presented early during treatment and were generally mild in nature.

The most common adverse drug reaction due to Stavudine was peripheral neuropathy (9%). Blake Max et al study[14] reported that incidence of peripheral neuropathy varies from 13-24%. Others studies had reported an incidence of peripheral neuropathy as 10%, 12 %.[15,16] From the study by Browne et al., quoted by Cherry et al.,[17] sensory neuropathy was the dose limiting toxicity of d4T and that the incidence of sensory neuropathy related to both the dose and duration of d4T.

Metabolic adverse reactions were common in d4T containing regimens.[18-20] In this study ADRs related to metabolism like Lipodystrophy and weight loss were also common with Stavudine based regimen(8%).ADRs related to Stavudine were presented late during treatment. The severity of ADR with d4T needed a change of regimen to AZT. Moreover, d4T requires monitoring for long-term metabolic changes, which may lead to morphologic disfigurements that are particularly distressing to females.

CONCLUSION

In summary, our study demonstrated that both the regimens were equally efficacious and no unexpected toxicity of either regimen was observed but there was difference presented between the regimens in ADRs

profile. Zidovudine based regimen presented with early occurring and mild ADRs while Stavudine related to late, well recognised and distressing toxicities. As the cost of both the regimens is now almost equal, preference should be given to AZT-based regimen.

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