

## RESEARCH ARTICLE

### Comparison of the efficacy and safety of 2 different antiretroviral regimens in tertiary care hospital: A retrospective observational study

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#### ABSTRACT

**Background:** Highly active retroviral therapy has reduced the morbidity and mortality of HIV infection. Although many regimens have reduced the plasma virus load in patients, there are many cases of long-term toxicity, adverse effects, and drug resistance. **Aims and Objective:** To compare the efficacy and safety between combination of stavudine lamivudine nevirapine (SLN) and stavudine lamivudine efavirenz (SLE) (antiretroviral regimens) in tertiary care hospital. **Materials and Methods:** A retrospective cohort study was conducted in the anti-retroviral therapy (ART) center of CG Hospital, a tertiary care center at Davangere. Data were collected for the duration of 12 months (June 2012 to May 2013). The study was conducted after obtaining the permission from the institutional ethical committee and incharge officer. Prescriptions of the patients were collected, and relevant information was entered in the preformed pro forma and analyzed. **Results:** In total of 144 cases, 94 patients received combination therapy of SLN whereas 50 patients received combination therapy of SLE. To compare the baseline parameters such as CD4 counts, weight and hemoglobin with post-treatment values Dunn's multiple comparison test was applied. To compare the changes in the parameters between the 2 therapies unpaired *t*-test was applied. There was a statistically significant improvement in CD4 counts in both the therapies but between group comparisons showed no statistical difference, inspite of clinical improvement more pronounced in patients receiving SLN combination. Hemoglobin levels have improved significantly post therapy in both the groups. **Conclusion:** In this study, there was clinically significant improvement in all the parameters considered for analyses in patients receiving SLN compared to SLE therapy but fails to show statistical significance.


**KEY WORDS:** Antiretroviral Regime; CD4 Count; Hemoglobin %

#### INTRODUCTION

According to UNAIDS 2010 report on the global AIDS epidemic, there are 33.3 million people living with HIV/AIDS in the world. As per the recent report of National

AIDS Control Organisation (NACO), the prevalence of HIV in India is 0.29% with total burden of 2.27 million HIV-infected patients. However, there has been decrease in the incidence of new HIV/AIDS cases in India after the introduction of a free ART program by NACO since April 2004.

Combined retroviral therapy has dramatically changed the course of HIV disease by reducing its morbidity and mortality.<sup>[1-4]</sup> Highly active anti-retroviral therapy (HAART) is effective in reducing the plasma viral load and in prolonging AIDS-free survival.<sup>[1,5,6]</sup> The availability of potent non-nucleoside reverse transcriptase inhibitors (NNRTI)

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based regimens may have several advantages for initial and prolonged therapy, fewer drug interaction, central nervous system penetration and more convenient administration with good adherence as they are given as 2 tablets twice a day, modestly priced, do not require food restrictions and safe during pregnancy.

Due to prolonged use of antiretroviral agents with incomplete viral suppression leads to the formation of drug-resistant viruses because of the extensive mutation rate of viruses. This is a major contributory cause of treatment failure.<sup>[7,8]</sup> This is a serious challenge in current clinical practice.

Since April 2002, fixed dose combination pill with 3 antiretroviral agents - stavudine, lamivudine, and nevirapine has been used in developing countries.<sup>[9]</sup> The World Health Organization (WHO, 2010 revision) guidelines recommend initiation of antiretroviral therapy with two NRTI (zidovudine or tenofovir disoproxil fumarate with lamivudine [3TC] or emtricitabine [FTC] and a NNRTI (efavirenz [EFV] or nevirapine).<sup>[10]</sup> Randomized clinical trials conducted in developed countries provide evidence that these regimens are safe and effective.<sup>[11,12]</sup> Efavirenz has recommended as one of the first drugs of choice and nevirapine as an alternative agent in initiation of antiretroviral treatment. In resource-poor settings, WHO has recommended nevirapine as one of the first drugs of choice in initiation of antiretroviral treatment. Although used since long non-randomized studies of both efficacy and tolerability of efavirenz and nevirapine in all possible therapeutic background are limited. Efavirenz-based HAART is still expensive in low and middle-income countries like India. Nevirapine is highly preferred over efavirenz by patients and treating consultants due to low cost and availability as fixed dose combination in tertiary care hospital. Adverse drug events are an important concern in ART. They can cause significant patient morbidity and are potentially fatal, are a common cause of drug discontinuation. Several systematic reviews reports a greater frequency of liver and skin toxicities associated nevirapine compared to efavirenz and greater frequency of CNS toxicity associated with efavirenz compared to nevirapine. A number of deaths attributed to toxicity was rare for both the drugs. Nevirapine will likely continue to be an important drug for the management of HIV-infected individuals and CNS associated side effects objective of the present study compare the efficacy and safety between combination of stavudine lamivudine nevirapine (SLN) and stavudine lamivudine efavirenz (SLE) (antiretroviral regimens) in tertiary care hospital.

## MATERIALS AND METHODS

### Study Design

A retrospective cohort study was conducted in the ART center of CG Hospital, a tertiary care center at Davangere.

Data were collected for the duration of 12 months (June 2012 to May 2013). The study was carried out after obtaining the permission from the institutional ethical committee. Permission was also obtained from officer incharge of ART center to access records. Prescriptions of the patients were collected, and relevant information was entered in the preformed pro forma and analyzed.

### Study Population

Patients eligible for inclusion in this study were those seen at the HIV Clinic between January 1, 2010, and September 30, 2012. We have included patients all the age groups. For inclusion in the study, patients had to be antiretroviral (ARV) naive and receiving their ARV medication through the Government HAART Program. Only patients who initiated treatment and compliant to a particular regimen for 6 months were evaluated. The patients excluded from the study are who initiated treatment with unreliable information on ARV history and baseline characteristics in such cases. Other patients excluded were those who were already in a second or subsequent HAART regimen on admission and whose CD4 values were not known at baseline.

### Study Setting

Outpatient at ART center of CG Hospital, a tertiary care center at Davangere.

### Sample Size

During the period of 12-month (June 2012 to May 2013), a total of 505 case sheets of patients diagnosed to have HIV-infection were collected.

### Informed Consent

Informed consent of the patients was taken, and data obtained were kept confidential.

### Statistical Analysis

In this study, data will be analyzed using descriptive statistics. Analysis to check for the changes after 6 months of treatment in parameters such as weight, hemoglobin, and CD4 counts was carried out. Paired *t*-test was applied to compare body weight and hemoglobin levels before treatment and after 6 months of treatment. Wilcoxon matched pairs signed rank test was applied to compare CD4 counts.

## RESULTS

Table 1 shows, as per objective of this study, we have divided patients into 2 treatment groups. Group A received combination of SLN and Group B received combination of SLE. In this study, total of 144 case records were evaluated. Of

those 94 cases had received SLN regimen whereas 50 cases received SLE combination therapy. Of 94 cases of SLN regimen, 16 cases belong to pediatric age groups ( $\leq 14$  years) of which 9 were males and 7 were females. Remaining 78 cases were of age group between 15 and 65 years of which 18 were males and 60 were females. Likewise patients receiving SLE combination had similar demographic data. Out of 50 patients of SLE treatment group, 4 cases belong to pediatric age groups ( $\leq 14$  years) of which 2 were males and 2 were females. Remaining 46 cases were of age group between 15 and 65 years of which 13 were males and 33 were females.

Females were more in both the groups. Community factors may have played the role as males might have more social stigma compared to females and females may be more aware of the disease in terms knowledge attitude and practice in receiving the treatment in timely manner.

Table 2 shows, according to disease control and prevention classification, disease can be divided into mild, moderate and severe based on baseline CD4 counts. In Group A, 4 patients have  $>500$  cells/ $\text{mm}^3$  when compared to 34 patients with CD4 counts between 200 and 499 cells/ $\text{mm}^3$  and 54 patients with cells  $<200/\text{mm}^3$ . Where as in Group B, 1 patient have CD4 count  $>500$  cells/ $\text{mm}^3$  when compared to 12 patients between 200 and 499 cells/ $\text{mm}^3$  and 37 patients with cells  $<200/\text{mm}^3$ .

**Table 1: Baseline data**

| Age group       | SLN (Group A) |       |         | SLE (Group B) |       |         |
|-----------------|---------------|-------|---------|---------------|-------|---------|
|                 | Total         | Males | Females | Total         | Males | Females |
| $\leq 14$ years | 16            | 9     | 7       | 4             | 2     | 2       |
| 15-65 years     | 78            | 18    | 60      | 46            | 13    | 33      |

SLE: Stavudine lamivudine efavirenz, SLN: Stavudine lamivudine nevirapine

**Table 2: CDC Classification**

| CD4 counts    | SLN (Group A) |       |         | SLE (Group B) |       |         |
|---------------|---------------|-------|---------|---------------|-------|---------|
|               | Total         | Males | Females | Total         | Males | Females |
| $>500$ cells  | 4             | 2     | 2       | 1             | 1     | 0       |
| 200-499 cells | 34            | 8     | 26      | 12            | 4     | 8       |
| $<200$ cells  | 54            | 16    | 38      | 37            | 10    | 27      |

SLE: Stavudine lamivudine efavirenz, SLN: Stavudine lamivudine nevirapine, CDC: Disease control and prevention

**Table 3: Comparing the parameters between Groups A and B**

| Parameters | SLN (Group A)     |                  |           | SLE (Group B)     |                  |           |
|------------|-------------------|------------------|-----------|-------------------|------------------|-----------|
|            | Baseline          | After treatment  | <i>P</i>  | Baseline          | After treatment  | <i>P</i>  |
| CD4 Counts | 162.5 (82.25-270) | 303 (197-455)    | $<0.0001$ | 111 (70.75-206.3) | 235 (162-370)    | $<0.0001$ |
| Hb levels  | 9.35 (8.1-11.18)  | 11.18 (9.8-2.15) | $<0.0001$ | 8.7 (7.7-10.2)    | 10.6 (10.2-11.7) | $<0.0001$ |
| Weight     | 42 (32.75-50)     | 45.00 (37-52)    | $<0.0001$ | 40 (35-45.25)     | 44.5 (37-50)     | $<0.0001$ |

SLE: Stavudine lamivudine efavirenz, SLN: Stavudine lamivudine nevirapine

The main efficacy parameter in our present study is the response to treatment which can be evaluated by knowing the increase in CD4 counts when compared to baseline and improvement in the Hemoglobin (Hb %) and Weight. Safety parameter we were looking for was the Hb % if it is reduced then the patient may be suffering with adverse effect due to treatment regimen that is anemia. Comparison of efficacy and safety of 2 different HAART regimen were carried out in this study.

All the parameters measured are expressed in Median with interquartile range (IQR). Table 3 shows, In Group A, baseline CD4 count is 162.5 (82.25-270) when compared to 6 months after treatment 303 (197-455) which was statistically significant with the  $P < 0.0001$ . In Group B, baseline CD4 count was 111 (70.75-206.3) when compared to 6 months after treatment 235 (162-370) which was statistically significant with the  $P < 0.0001$ .

Another efficacy parameter assessed was the weight (kg). In Group A, 42 (32.75-50) after treatment compared to 45 (37-52) at baseline which was statistically significant ( $P < 0.0001$ ). In Group B, 44.5 (37-50) compared to 40 (35-45.25) at baseline which was statistically significant ( $P < 0.0001$ ).

Hb % which we have considered as efficacy and safety parameter showed significant increase that is median and IQR 11.18 (9.8-12.12) after 6 months of Group A treatment when compared to baseline value 9.35 (8.11-11.18) which was statistically significant ( $P < 0.0001$ ). Similarly, Group B values were 8.7 (7.7-10.2) at baseline when compared to 10.6 (10.2-11.7) after 6 months of treatment which was statistically significant ( $P < 0.0001$ ).

The difference between the 2 groups that is patients receiving SLN and SLE were compared using unpaired t test in terms of efficacy and safety, but there was no significant difference between the groups. Hence, both the treatments are equally efficacious with better tolerability.

To address the query of the magnitude of response to treatment in severely ill patients between the groups, we have considered the patients who have poor baseline CD4 counts that is  $<200$  cells/ $\text{mm}^3$  and their response to treatment in terms of 3 different parameters, i.e., CD4 counts, weight and Hb%. Comparing efficacy and safety of 2 regimen

in severely ill patients with HIV infection (CD4 counts <200 cells/mm<sup>3</sup>).

As shown in Table 4, in severely ill patients of SLN groups baseline CD4 counts were 98 (50.5-42.3) when compared to 221.5 (157-315.5) after treatment and in SLE groups baseline CD4 counts were 85 (61-129) when compared to 202 (151.5-252) after treatment. Unpaired t test was applied to compare difference between the 2 groups in response to treatment. There was no statistically significant difference between 2 treatment groups. Likewise Hb % and weight between 2 groups were compared, and there was no statistically significant difference between the 2 groups.

## DISCUSSION

In this study, there was no significant between the 2 groups in terms of efficacy and safety, i.e., CD4 counts increased in both the groups to a similar extent compared to baseline values. Likewise weight and Hb % showed similar improvement in both treatment groups. However, there was clinically significant improvement in all the parameters considered for analyses in patients receiving SLN compared to SLE therapy but fails to show statistical significance.

An observational non-randomized study done by Patel et al. in India taking nevirapine and efavirenz based HAART regimens showed comparable immunological response in naïve HIV 1 infected with more rash and hepatotoxicity with nevirapine and CNS side effects with efavirenz. In developing countries like India, nevirapine is a good alternative to efavirenz with comparable immunologic effectiveness. Side effect profile must be kept in mind while choosing any NNRTI based regimen.<sup>[13]</sup>

A randomised open-label trial done by F van Leth et al. concluded that antiretroviral therapy with nevirapine or efavirenz showed similar efficacy, so triple-drug regimens with either NNRTI are valid for first-line treatment. There are, however, differences in safety profiles. Combination of nevirapine and efavirenz did not improve efficacy but caused more adverse events.<sup>[14]</sup>

Meta analyses done by Siegfried et al. concluded that the combination of nevirapine, 3TC and d4T is as efficacious as a combination of efavirenz, 3TC and d4T. Once-daily NVP with twice-daily 3TC and d4T is as efficacious as twice-daily

NVP, 3TC and d4T. However, toxicity may be increased in the once-daily NVP regime. Additional trials of sufficient duration are required to provide better evidence for the use of this combination as a first line therapy. Ideally, trials should use standardized assessment measures especially with respect to measuring viral load so that results can be compared and combined in meta-analyses.<sup>[15]</sup>

They also suggested that additional trials of sufficient duration are required to provide better evidence for the use of SLN as a first line therapy. Ideally, trials should use standardised assessment measures, especially with respect to measuring viral load, so that results can be compared and combined in meta-analyses. Assessment of fixed-drug dosing is required in the context of a trial. Clinical studies assessing the rate of adverse events, and resistance of the SLN regimen, continue to be required to better inform practice (Siegfried et al., 2011).

Motivating the community health-care systems to work in combined approach for early diagnosis of HIV and instituting treatment with triple regimen will help in reducing the disease burden. The responsibility of community health-care system does not end here as it is the compliance that matters the most for the successful drug therapy. Community health-care workers must be appointed to check for compliance and enquire about difficulty in taking medications. Psychological reassurance will make the patient more adherent to the treatment.

## CONCLUSION

HIV is a communicable disease which can be controlled by early diagnosis followed by institution of triple HAART in timely manner, watching for compliance by community-based approach and good social environment to cop up with the disease. Comparing the response in severely ill patients to treatment between the 2 regimens, an increase CD4 count was observed in both the groups to similar extent. Hb% and weight also have shown a similar response to treatment of both the regimen. Thus, we can suggest that investing on expensive efavirenz regimen and preferring it over nevirapine-based regimen will do little good. Nutritional supplementation with good rest for the patients will make a great impact on health outcomes as we show there was an improvement in Hb% and weight in our study, but still the patients were anemic and underweighted. Providing social

**Table 4:** Comparing parameters in severely ill patients

| Parameters | SLN (Group A)   |                   | SLE (Group B)    |                  |
|------------|-----------------|-------------------|------------------|------------------|
|            | Baseline        | After treatment   | Baseline         | After treatment  |
| CD4 counts | 98 (50.5-42.3)  | 221.5 (157-315.5) | 85 (61-129)      | 202 (151.5-252)  |
| Hb levels  | 9.2 (7.8-11.03) | 11.20 (9.6-12.20) | 8.75 (7.7-10.25) | 10.9 (10.2-11.8) |
| Weight     | 40 (32.75-50)   | 45 (37-51.75)     | 40 (35-46)       | 45 (37-50.5)     |

SLE: Stavudine lamivudine efavirenz, SLN: Stavudine lamivudine nevirapine



incentives by accepting them into the community where they are living without isolation will improve the patient's well-being and health outcomes.

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