

Evaluation of efficacy of two drug regimens of anti-retro viral therapy**Sachidananda Adiga M. N.¹, B. N. Malawadi², Usha S. Adiga^{2*}**¹Department of Pharmacology,²Department of Biochemistry,
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medium, provided the original
work is properly cited.**ABSTRACT****Background:** CD4 count is an important marker to assess the effectiveness of treatment, mortality and survival rates in HIV patients on treatment. It is an important guide to treatment as it reflects drug resistance, treatment failure and need to switch over to different regimen. Objective of the study was to assess the efficacy of tenofovir (TDF) and efavirenz (EFV) versus zidovudine (AZT) and nevirapine (NVP), in combination with lamivudine (3TC) in HIV-infected patients taking basal and after treatment CD4 count levels as tools.**Methods:** A retrospective observational study on 40 adult HIV patients, receiving AZT+3TC+NVP (ZLN) (group I) and 18 patients on TDF+3TC+EFV (TLE) (group II) was carried out. Demographic profile, medication prescribed, baseline CD4 cell counts, serially monitored CD4 count values and Hb% were recorded from patient's medical record. Student's paired 't' test was done to compare CD4 counts before and after treatment in individual groups. Unpaired 't' test was used for the comparison of CD4 counts between the groups.**Results:** A very highly significant ($p < 0.0001$) increment in CD4 count was observed in group I after treatment. Improvement in CD4 count was highly significant in group II as well with $p < 0.0004$. The extent of improvement was significantly better ($p < 0.05$) in group I as compared to group II. Patients in group I were better staged clinically.**Conclusions:** We conclude that ART regimen containing AZT/3TC/NVP is proved to be superior to TDF/3TC/EFV. However further studies need to be done, by taking drug adherence into account in a larger patient population.**Keywords:** CD4 Count, Efavirenz, Nevirapine, Tenofovir, Zidovudine**INTRODUCTION**

The highly active antiretroviral therapy (HAART) has led to a significant reduction in acquired immune deficiency syndrome (AIDS) related morbidity and mortality. Access to antiretroviral therapy (ART) has improved tremendously over the last few years due to implementation and enforcement of various strategies by national AIDS control organization (NACO) in India. NACO has established ART centres in selected government hospitals which offer free treatment for HIV/AIDS and related opportunistic infections.¹ In India NACO offers systematic HIV care by providing drugs free of cost, a detailed counseling algorithm for psychosocial support and management of adverse reactions, with a special emphasis on adherence to ART.

The treatment of HIV infection and AIDS is complex because of many reasons. The variety of tailor made ART regimens considering many associated factors, duration of treatment, adherence to treatment and opportunistic infections associated are the main contributing factors for the complexity of treatment. Besides that, adverse drug reactions (ADRs) related to ART use makes the treatment still more challenging. Studies have shown that nearly 25% of all patients discontinue their initial HAART regimen because of treatment failure, adverse drug reactions, noncompliance within the first eight months of therapy.^{2,3}

The sustained benefits of HAART have led to far greater numbers of HIV-1 infected cases receiving at least three drugs for greater periods of time. Highly active antiretroviral therapy (HAART), currently recommended is the cornerstone of management of patients with HIV infection. Nucleoside reverse transcriptase inhibitor (NRTI) like zidovudine (AZT) and nucleotide reverse transcriptase inhibitor (NtRTI) like tenofovir (TDF) are the most common medications given in first-line ART.

WHO treatment guidelines postulate a 'minimum package' of laboratory monitoring that includes an initial CD4 cell count prior to HAART, which should be repeated at least twice a year in treated patients.^{4,5} Efficacy of various regimens can be compared by taking CD4 count, viral load as the tool of assessment.

This study was conducted to evaluate the efficacy of tenofovir and efavirenz (EFV) versus zidovudine and nevirapine (NVP), in combination with lamivudine (3TC) in HIV-infected patients taking basal CD4 counts and after treatment CD4 counts as tools of comparison as there are only a few published data available regarding the efficacy of above two regimens.

METHODS

A retrospective observational study on 40 adult HIV patients, receiving AZT+3TC+NVP (ZLN) (group I) and 18 patients on TDF+3TC+EFV (TLE) (group II) was carried out in Karwar Institute of Medical Sciences, Karwar. Data of patients who were diagnosed to be HIV positive, receiving HAART and were attending the hospital for regular follow up once in six months was collected. Patients receiving above mentioned regimens at least for six months were included and those with less than six months of treatment were excluded. Patients were evaluated in detail by measuring CD4 count, both basal as well as serial measurements once in 6 month, hemogram and other laboratory parameters.

Data was extracted from patient's medical records using data collection form. Patient demography such as age, gender, medication prescribed (drug regimen), baseline CD4 cell counts, serially monitored CD4 count values (once in 6 months) and Hb% were recorded.

Patients in group I am in the age group of 39.84 ± 8.01 years and consist of 65.79% males and 34.21% females. They were receiving a standard drug dosage of AZT 300 mg twice daily, 3TC 150 mg twice daily or 300 mg once daily, NVP 200 mg once daily for a 2-week lead-in period and then as 200 mg twice daily. Mean duration of the treatment is 4.51 ± 2 years. Hemoglobin is 12.21 ± 0.37 gm%.

Group II had patients in the age group of 37.61 ± 9.29 years, 33.33% of them being males and 66.67% of them being females. They were on a standard drug dosages, TDF 300 mg once daily, 3TC 150 mg twice daily or 300

mg once daily and EFV 600 mg once daily. Mean duration of their treatment was 2.64 ± 2.1 years. Hemoglobin was 10.96 ± 0.58 gm%.

The present study assessed the efficacy of two regimen containing TDF/EFV versus AZT/NVP, 3TC being common in both the regimens in HIV patients. Basal CD4 count and improvements in CD4 counts in subsequent follow up visits being the tool to compare and measure the efficacy of the two regimens. CD4 count was measured by flow cytometric method. Patients of both the groups were staged as per WHO clinical staging guidelines, after receiving treatment (Table 1).

Table 1: WHO clinical staging of HIV patients on treatment.

Clinical stage	CD4 count cells/cmm
I	>1200
II	500-1200
III	200-500
IV	<200
V	<50

Statistical analysis was done by descriptive statistics using suitable softwares. Student's paired 't' test was done to compare CD4 counts before and after treatment in individual groups. Unpaired 't' test was used for the comparison of CD4 count and mean hemoglobin between the groups. Statistical significance was fixed at level 0.05.

RESULTS

Distribution of CD4 counts before and after therapy was represented in Figure 1 for group I and Figures 2 for group II. Basal CD4 count was 243.78 ± 23.58 cells/cmm in patients receiving AZT/3TC/NVP and they had a follow up count of 422.6 ± 56.7 . Patients in group II (TDF/3TC/EFV) had basal CD4 count of 168.86 ± 50.7 and CD4 count of 262.2 ± 60.4 after treatment.

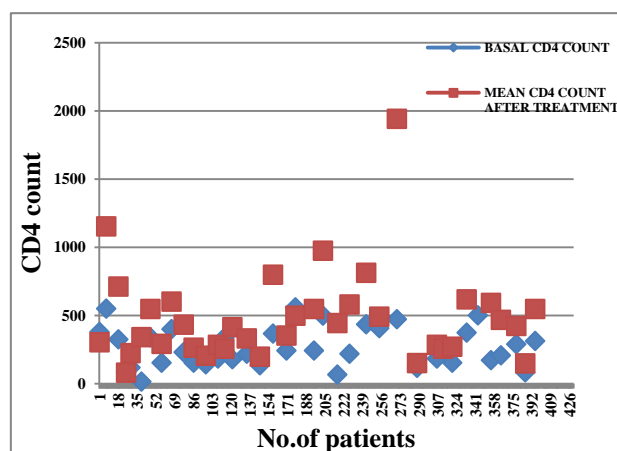


Figure 1: CD4 count before and after treatment with ZLN regimen (AZT+3TC+NVP).

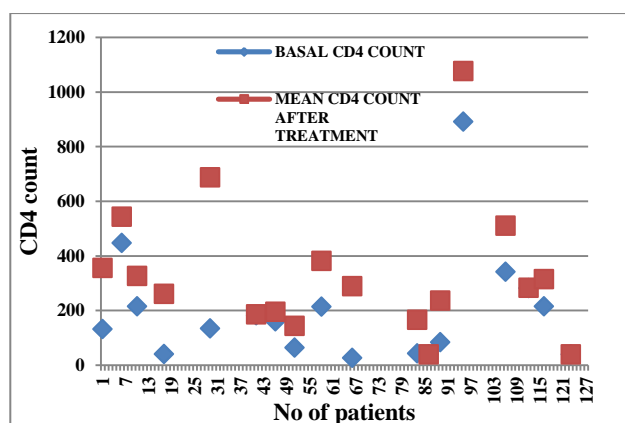
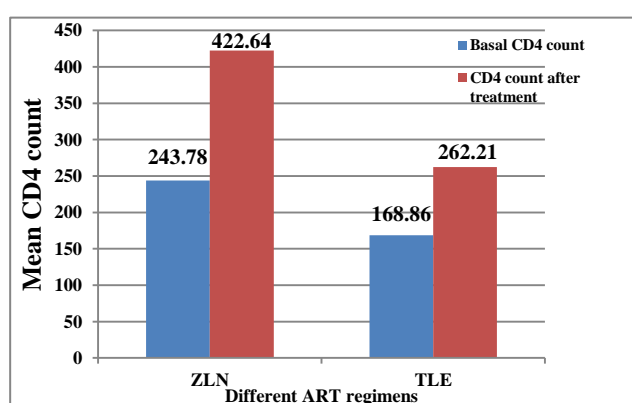


Figure 2: CD4 count before and after treatment with TLE regimen (TDF+3TC+EFV).



*Group I, $p < 0.0001$, Very highly significant (ZLN); † Group II $p < 0.004$ Highly significant (TLE).

Figure 3: Comparison of CD4 counts before and after treatment in two regimens.

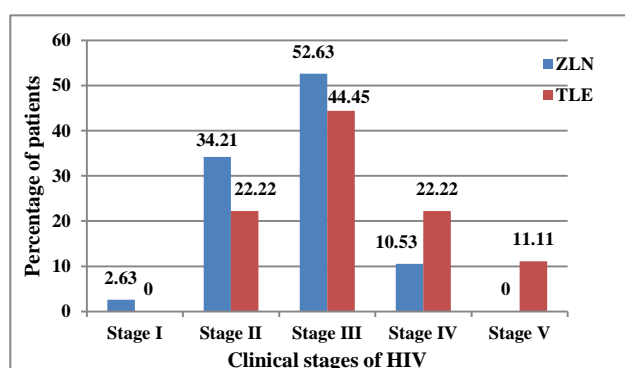


Figure 4: Comparison of WHO clinical staging of patients on two regimens.

The comparison of basal CD4 count and follow-up CD4 count between the two groups were given in Figure 3. A very highly significant ($p < 0.0001$) increment in CD4 count was observed in group I after treatment. Improvement in CD4 count was highly significant in group II as well with $p < 0.0004$ (Figure 3).

Comparison of distribution of number of patients (in percentage) in different clinical stages based on CD4 counts in two groups after treatment was shown in Figure 4.

DISCUSSION

There was 73% elevation in CD4 count in group I as compared to 55% in group II after treatment. Improvement in CD4 count was significant was better in group I compared to group II. It was also evident from our study that clinically patients of group I were better staged according WHO clinical staging guidelines as compared to those in group II (Figure 4). Percentages of patients are more in stage I, II and III for group I whereas majority of group II patients lie in stage IV and V. Thus we can conclude from our study that regimen containing AZT/3TC/NVP is more effective than that containing TDF/3TC/EFV.

We have come across hardly a few similar reports from the literature which compares these two regimens to the best of our knowledge. But we have a good number of studies comparing AZT versus TDF and NVP versus EFV. A study by Emnet et al reported that patients with TDF had greater increase in CD4 count from baseline compared to patients with AZT during the first year of treatment. Subsequently during follow up, there was no significant difference in CD4 counts between the drugs. But patients receiving TDF had higher mean CD4 count.⁶ However this report does not support our study.

If we take mean hemoglobin level as the tool to compare two regimens, we have statistically significant high mean Hb% in group I patients as compared to group II (Table 2). Regimen containing AZT is proved to be superior to that containing TDF. However we have not matched the duration of the therapy.

TDF containing regimen in first-line treatment instead of AZT in resource-limited settings is very cost-effective. It might preserve future treatment options in absence of virological monitoring. Cost effectiveness analyses have pointed towards better clinical outcomes with TDF use compared with other NRTIs in industrialized and resource-limited settings.⁷⁻¹¹

There is also a report supporting tenofovir use could improve regimen durability and treatment outcomes in resource-limited settings.¹²

When we consider NVP versus EFV, literature suggests that EFV has shown to be equivalent or superior to NVP.¹³⁻¹⁵ NVP is the most widely available NNRTI in low- and middle-income countries, thus most of the studies in resource limited settings have focused on comparing EFV versus NVP. But in our study, regimen containing NVP is found to be superior. Compared to NVP, EFV may show a slight benefit in terms of toxicity and adverse drug reactions.

Even though individually TDF and EFV are proved to be beneficial over AZT and NVP, effectiveness of the treatment depends on various factors like associated co-infections, co-morbid conditions, adverse drug reactions, poor drug compliance, poor drug adherence etc. Low efficacy of TDF regimen observed in our study could be attributed to above mentioned reasons. Concomitant medications have a vital role in determining the effectiveness of the regimen.

Several studies have reported that 25% of patients discontinue initial HAART regimen because of treatment failure, toxic effects or noncompliance within the first eight months of therapy.^{2,3} This could also be the contributing factor to poor outcome in group II patients. We could have thrown more light on this had we considered treatment adherence into account.

CONCLUSION

We conclude that ART regimen containing AZT/3TC/NVP is proved to be superior to that containing TDF/3TC/EFV. However further studies need to be done in this area, by taking adherence to treatment, concomitant infections, adverse reactions which lead to poor drug compliance in a larger population of patients to explore more information.

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