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A comparative evaluation of the effects of ZLN and TLE anti-retroviral regimens in HIV positive patients: A retrospective record-based study

Ritika Singla[1], Neetu Sharma[2]

[1]Department of Pharmacology, All India Institute of Medical Sciences, Bathinda, [2]Department of Pharmacology, Government Medical College, Patiala, Punjab, India.

***Corresponding author:**
Ritika Singla,
Department of Pharmacology,
All India Institute of Medical Sciences, AIIMS, Bathinda - 151 001, Punjab, India.

singla.ritika1308@gmail.com

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ABSTRACT

Objectives: Until 2012, zidovudine+lamivudine+nevirapine (ZLN) was the first line treatment for human immunodeficiency virus (HIV)-positive patients, whereas in 2013, tenofovir+lamivudine+efavirenz (TLE) was recommended as a preferred regimen due to less adverse drug reactions and better virological response. The present study was done to compare the change in CD4 count and emergence of opportunistic infections (OIs) in HIV-positive patients on ZLN and TLE regimens.

Materials and Methods: This retrospective record-based study was conducted at anti-retroviral therapy (ART) center of a tertiary care hospital on 150 charts of patients on ZLN (Group A) and TLE (Group B) regimens each for 1 year. Data were analyzed using GraphPad Prism version 6.

Results: The mean age of patients in Group A was 38.72 (±10.5) years and Group B 37.75 (±11.57) years ($P = 0.4460$). After 1 year of ART, the mean CD4 count (cells/mm^3) increased in both groups (Group A: 223.51 [±111.21] to 415.37 [±218.16] [$P = 0.0001$] vs. Group B: 255.05 [±164.50] to 433.12 [±247.66] [$P = 0.0001$]). With the baseline counts being comparable ($P = 0.0527$), the difference in mean CD4 counts between the groups post-ART was not statistically significant ($P = 0.5105$). The incidence of OI was 45% in Group A as compared to 25% in Group B. Overall, the most prevalent OI was tuberculosis (TB) (13.33%).

Conclusion: Both ZLN and TLE regimens are equally effective in improving the immunological status of HIV-positive patients. Patients on ZLN have higher incidence of OI than those on TLE. However, therapy should be individualized as per patient's suitability.

Keywords: Human immunodeficiency virus, CD4 count, Opportunistic infections, Anti-retroviral therapy

INTRODUCTION

The acquired immune deficiency syndrome (AIDS), also called "slim disease," is caused by human immunodeficiency virus (HIV) which slowly breaks down the body's immune system, leaving the victim vulnerable to many life-threatening opportunistic infections (OI), neurological disorders, and unusual malignancies.[1]

India has 2.1 million people living with HIV, which is the third-largest population of people infected with the virus. Around 36% of Indian adults with the virus have access to anti-retroviral therapy (ART).[2] One of the most striking and consistent immunological features of HIV is the progressive reduction in the CD4 cell counts.[3] The risk of OI increases as the CD4+ cell count decreases.[4]

In India, National AIDS Control Organisation (NACO) has implemented and enforced various strategies to improve the access to ART.[5] Free ART has been available in India since 2004 with facilities such as HIV testing and counseling (HTC), nutritional advice and treatment for HIV, and OI. CD4 counts are tested every 6 months.[6]

Zidovudine (AZT), a deoxythymidine analog, is well absorbed and has myelosuppression as the most common adverse drug reaction (ADR). It also crosses the blood–brain barrier (BBB).[7] Lamivudine (3Tc), a deoxycytidine analog, has mild ADRs such as headache and gastrointestinal discomfort.[8] Nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is metabolized by the CYP3A enzymes and can induce its own metabolism. It crosses BBB and placenta so is used in pregnancy to prevent mother to child transmission. Rash is a common ADR.[9] Tenofovir (TDF), a nucleotide reverse transcriptase inhibitor (NRTI), can cause growth restriction, bone deformities, and renal tubular dysfunction with prolonged therapy.[5] Efavirenz (EFV) is a NNRTI with a long half-life (40–55 h). It is advised to be taken empty stomach as increased bioavailability after a fatty meal can lead to toxicity mainly involving central nervous system. It is contraindicated in pregnancy, especially in the first trimester.[10]

The World Health Organization (WHO) 2013 guidelines recommend a preferred treatment regimen of TDF+3TC+EFV (TLE), or TDF+emtricitabine (FTC)+EFV, as a fixed-dose combination (FDC) due to less ADRs and better virological response than once- and twice-daily options currently available.[11]

Accordingly, the first-line treatment has seen a shift from previously preferred ZLN (AZT+3TC+NVP) to TLE. Literature search provides few comparative studies of these two regimens. This study aims to compare the efficacy of ZLN and TLE regimens in HIV-positive patients and the emergence of OI in patients while on ART.

MATERIALS AND METHODS

Study design

This was a retrospective observational record-based study of HIV-positive patients undergoing treatment with ZLN and TLE regimens in the ART center of a tertiary care hospital of North India. The data were collected for a period of 1 year. This study was registered with Clinical Trials Registry of India (CTRI/2017/03/008086).

Study population

A total of 300 treatment charts of HIV-positive patients fulfilling inclusion and exclusion criteria were reviewed. It included 150 charts of patients on ZLN and TLE regimens each. Group A included charts of patients receiving ZLN (zidovudine 300 mg + lamivudine 150 mg + nevirapine 200 mg) twice a day and Group B included charts of patients receiving TLE (tenofovir 300 mg + lamivudine 150 mg + efavirenz 600 mg) once a day.

Inclusion criteria

The following criteria were included in the study:

1. Adults above 18 years
2. Patients receiving the treatment with standard ZLN and TLE drug dosages for at least 1 year and attending the hospital for regular follow-up once in 6 months
3. HIV patients with TB, ARI, and other OI
4. Patients receiving cotrimoxazole preventive therapy

Exclusion criteria

The following criteria were excluded from the study:

1. Pregnant and lactating women
2. Patients on ART for <1 year
3. Patients requiring dose adjustments in the standard ZLN and TLE treatment regimens
4. Records with incomplete data

Chart assessment

A treatment chart of a HIV-positive patient has the information regarding identity of the patient including name, age, sex, occupation, address, and ART registration number; family history of the patient including parents, spouse, and children with their HIV status; possible cause of HIV infection (heterosexual, unsafe injection, blood transfusion, needlestick injury, etc.); details of ART including date of registration, date of initiation of therapy, current ART regimen and shuffling of ART regimens, treatment record, adherence to therapy, any ADRs, and any rescue treatment; CD4 counts at the time of registration and every 6 months thereafter; other laboratory investigations such as hemoglobin, total leukocyte count; and any OI including full details of tuberculosis (TB), and status of hepatitis C, hepatitis B, and sexually transmitted diseases.

Of all the available information from the chart, details of the patient's identity were not noted. Age of the patient and date of initiation of therapy were assessed along with improvement in CD4 counts of patients on ART after 1 year of initiation of treatment and prevalence of OI was noted.

All medical records and research materials were kept confidential and not made publicly available and were only used for the purpose of the research study. The identity of patients was never disclosed. The study was conducted after approval from the Institutional Ethics Committee.

Statistical analysis

All the data were analyzed using GraphPad Prism version 6.0. P <0.05 was considered to be statistically significant.

RESULTS

A total of 300 treatment charts of HIV-positive patients on ART were reviewed. The mean age of the patients was 38.23 years. The mean age of the patients in Group A was 38.72 (±10.5) years while in Group B was 37.75 (±11.57) years. Statistically, there was no significant difference in the mean age of both the groups (P = 0.4460) [Table 1].

Within-group comparison of CD4 counts was done by paired t-test. The mean baseline CD4 count of patients in Group A was 223.51 (±111.21) cells/mm^3. After 1 year of therapy, the CD4 counts increased from the mean baseline values to a statistically significant mean value of 415.37 (±218.16) cells/mm^3 (P < 0.0001; 95% CI [160.59–223.11]). Similarly, in Group B, 1 year of therapy with TLE regimen increased the CD4 count from mean baseline of 255.05 (±164.50) cells/mm^3 to a mean value of 433.12 (±247.66) cells/mm^3. These results were seen to be statistically significant (P < 0.0001; 95% CI [149.53–206.62]) [Table 2].

Between the groups comparison of CD4 counts was done by unpaired t-test. The mean baseline CD4 counts of the two groups were comparable, that is, not statistically different (P = 0.0527; 95% CI [0.37–63.44]). The CD4 counts increased by 191.85 cells/mm^3 in patients on ZLN regimen and by 178.07 cells/mm^3 in patients on TLE regimen. The mean CD4 counts after 1 year of ART were 415.37 (±218.16) cells/mm^3 in those on ZLN and 433.12 (±247.66) cells/mm^3 in those on TLE regimen. The difference between the two means was not statistically significant (P = 0.5105; CI [35.28–70.79]), that is, both the regimens had almost equal efficacy in terms of increase in CD4 counts [Table 2].

The incidence of OI was 45% (67 patients) in Group A and 25% (37 patients) in Group B. Overall, TB (13.33%; 40 patients) was the most prevalent OI seen followed by recurrent respiratory infections (ARI) 8% (24 patients) and candidiasis 7.33% (22 patients). The most prevalent OI in Group A was ARI 14.67% (22 patients) and in Group B was TB 18% (27 patients) [Table 3].

Table 1: Distribution of patients according to age (years).

Age (years)	% of patients
≤30	29
31–40	36.33
41–50	23
≥50	11.67

DISCUSSION

Due to the shift from ZLN to TLE as the first-line antiretroviral regimen of choice, the study ought to compare the efficacy of the two regimens which is one of the major concerns in the treatment of HIV/AIDS. The study presents the same by comparing the change in CD4 count after 1 year of therapy and prevalence of OI while on ART.

Although viral load is considered as a better marker to monitor the effectiveness of therapy after initiation of ART, CD4 count was taken as a one of the parameters for the efficacy of ART in this study. CD4 count is considered to be an important marker in evaluating the effectiveness of treatment. It also helps in guiding the treatment as it can indicate the resistance to drugs and failure of therapy and hence the need to switch from one regimen to another.[12] As indicated by Mellors *et al.*, CD4 count stands next only to

Table 2: Within the group and between the group comparison of CD4 counts before and after 1 year of ART.

	Group A		Group B		Baseline		After ART	
	Baseline	After ART	Baseline	After ART	Group A	Group B	Group A	Group B
n	150	150	150	150	150	150	150	150
Mean (cells/mm^3)	223.51	415.37	255.05	433.12	223.51	255.05	415.37	433.12
SD	111.21	218.16	164.50	247.66	111.21	164.50	218.16	247.66
SEM	9.08	17.81	13.43	20.22	9.08	13.43	17.81	20.22
t	12.1268		12.3268		1.9450		0.6588	
df	149		149		298		298	
Two-tailed P value	0.0001*		0.0001*		0.0527**		0.5105**	
Mean difference	−191.85		−178.07		31.53		17.75	
Std. error difference	15.821		14.446		16.213		26.948	
95% CI of the diff.	160.59–223.11		149.53–206.62		0.37–63.44		35.28–70.79	

*P<0.05 both in Group A and Group B after 1 year of ART by paired t-test. **The baseline CD4 count was comparable between the two groups and the difference was not significant after 1 year of therapy by unpaired t-test. Group A: ZLN, Group B: TLE, ART: Anti-retroviral therapy, N: Number of patients, SD: Standard deviation, SEM: Standard error of mean, t=t-statistic, df: Degree of freedom, Std.: Standard, CI: Confidence interval

Table 3: OI incidence comparison between ZLN (Group A) and TLE (Group B) during ART.

	ZLN (%)	TLE (%)
TB	13 (8.67)	27 (18)
ARI	22 (14.67)	2 (1.30)
Candidiasis	16 (10.67)	6 (4)
Multiple organ involvement	12 (8)	1 (0.67)
Hepatitis C	1 (0.67)	1 (0.67)
Diarrhea	2 (1.33)	0
Herpes	1 (0.67)	0
Total	67 (45)	37 (25)

OI: Opportunistic infection, TB: Tuberculosis, ARI: Recurrent respiratory infection

plasma viral load as the best predictor of disease progression to AIDS and mortality but the prognosis and survival of HIV-positive patients are better estimated by measurement of both plasma viral load and CD4 count together.[13] As mentioned in the guidelines for the use of anti-retroviral agents in HIV-positive adults and adolescents published in 2016, CD4 count is the most important laboratory parameter to assess the immune response of the patient to ART and also helps in determining the need to initiate ART and prophylaxis for OI.[14] Furthermore, CD4 count testing is cheap and is provided free of cost at ART centers in India. At present, in India, people living with HIV on ART are monitored with CD4+ T lymphocyte count every 6 months. Viral load testing was earlier carried out as targeted viral load testing, when the individuals showed immunological failure during follow-up. In 2018 National guidelines for HIV-1 viral load laboratory testing, NACO formulated algorithms on the routine HIV-1 viral load testing for the monitoring of HIV-1-infected individuals.[15]

This study shows that the two regimens are equally effective in increasing the CD4 counts of HIV-positive patients. There are limited studies available in the literature comparing these two regimens in the North Indian population. The findings of our study match with those of a study conducted by Hemasri *et al*. in a sample size of 400 cases.[6] A combined prospective and retrospective study by Krishnan and Sajeeth also reported relatively similar efficacy in both the regimens.[3] This is in contrast to the findings of a study by Adiga *et al*. which reported ZLN regimen to be more effective than TLE with statistically significant increase in CD4 count with ZLN than with TLE.[12] However, this study was conducted on a small sample size of 40 patients on ZLN and 18 patients on TLE, so the comparison of efficacy between the two regimens might not have been accurately determined.

The literature has studies comparing the efficacy of EFV containing and NVP containing regimens. One such study by Adiga *et al*. reported significantly higher increment in CD4 count in patients on EFV containing than those on NVP containing regimen.[16] Combination of a drug with another in a regimen strongly determines the effectiveness of that regimen, even though individually a drug might prove efficacious over the other. Moreover, multiple factors such as adherence to therapy, comorbid conditions, and ADRs determine the effectiveness of a treatment. This could possibly be the reason of contrary findings of this study with our study.

The prevalence of OI was found to be higher in the patients on ZLN than in patients on TLE and overall, the most prevalent OI seen was TB followed in line by ARI and candidiasis. Krishnan and Sajeeth also reported OI to be more prevalent in patients on ZLN/E than on TLN/E with ARI as the most common OI in both the groups.[3] Our study, however, reported ARI to be the most common in patients on ZLN and TB to be most common OI in patients on TLE. Pulmonary infections (70%), not only the AIDS-related OI, are currently the leading cause of morbidity and mortality and the first cause of hospital admissions in HIV-infected people. Lower respiratory tract infections are known to be 25-fold more prevalent in HIV patients than in the general population.[17] The occurrence of any type of OI in HIV patients during follow-up depends on multiple variables such as sociodemographic characteristics, WHO clinical stage, CD4 count, prior history of OI, past OI prophylaxis, the baseline ART regimen, adherence to ART, side effects of ART, and treatment failure. Of these, the WHO clinical stage, CD4 count, past OI prophylaxis, and adherence to ART have been shown to be the strongest predictors of the occurrence of OI.[18] Further studies are recommended to look for the association between the type of ART regimen and the prevalence of OI after adjusting for the multiple independent variables.

Studies have shown that nearly 25% of all patients discontinue their initial HAART regimen because of treatment failure, ADRs, and non-compliance within the first 8 months of therapy.[5] More could have been discussed in this matter if the safety and adherence to the treatment were assessed in this study.

The retrospective nature is the main limitation of our study. A well-planned prospective study with stringent inclusion and exclusion criteria could better depict the comparative changes in CD4 count and the incidence of OI with ART. We did not take into account the sociodemographic characteristics, adherence of the patients to the therapy, and also the incidence of ADRs with the two regimens which influence the compliance and hence the response to the treatment.

CONCLUSION

From the findings of our study, we conclude that both ZLN and TLE regimens are equally effective in improving the

immunological status of HIV-positive patients. The incidence of OI was seen to be higher with ZLN than that with TLE. The therapy should be individualized according to the patient's need, occurrence of OI and ADRs with a particular regimen, and the best suited therapy. It is suggested that more research be carried out in this area taking into account the adverse effects which play a major role in determining the compliance of the patient to therapy.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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