Research Article

Comparison of two zidovudine based HAART regimens used in treatment of HIV infection

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ABSTRACT

Background: India has third highest number of HIV patients. Zidovudine based regimens are the first line of treatment in these patients. This study was undertaken to compare three prognostic markers with this treatment in patients infected with HIV. The objective of the study was to compare the changes in the CD4 counts, hemoglobin and weight between HIV infected patients receiving zidovudine, lamivudine and nevirapine (ZLN) against those receiving zidovudine, lamivudine and efavirenz (ZLE).

Materials and Methods: Retrospective data was collected from the ART centre, Chigateri Hospital, Davangere. Patients who were on the study regimens for atleast six months were considered for analysis. Changes in CD4 counts, hemoglobin levels and weight were analyzed with paired 't' test for intra group variation and unpaired 't' test for intergroup variation.

Results: CD4 counts were analyzed in 339 patients and in both the groups the counts improved significantly (ZLN: n=252, ZLE: n=87 and $p < 0.001$ in both groups) after six months of treatment but the improvement was much better in patients who received ZLN regimen ($p = 0.005$). 281 patients were analyzed with respect to hemoglobin and improvement was seen in ZLE group (n=77, $p = 0.001$) but not in ZLN group (n=204, $p = 0.36$) with treatment and intergroup analysis was in favor of ZLE ($p = 0.03$). Weight was analyzed in 356 patients and it improved significantly in both ZLN group (n=264, $p = 0.001$) and ZLE group (n=92, $p = 0.001$) but the intergroup comparison did not reveal any significance ($p = 0.21$).

Conclusion: A regimen consisting of zidovudine, lamivudine and efavirenz is better in treating a HIV patient with decreased hemoglobin. So this regimen can be preferred in anemic patients with HIV.

Key words: HAART, zidovudine, lamivudine, nevirapine, efavirenz.

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INTRODUCTION

70 million people worldwide have been infected by this virus and its subtype, HIV 2, killing nearly 35 million people. The incidence is varied in different regions of the world. The sub-saharan Africa is the region that bears the highest burden of this disease currently with one in every twenty adults living with HIV-AIDS. In India, the first case with HIV was reported in the year 1986. Since then the epidemic has grown. As per the latest census there are about 23.9 lakh people living with HIV/ AIDS(PLHA) in our country.[1]

Recognizing this as a global health problem, United Nations General Assembly emphasized the need for Anti-retroviral therapy (ART) in June 2001. In April 1992, the World

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Health Organisation released the guidelines for the use of ART in resource constrained settings. A plan of scaling up the programme to cover atleast 3 million people by the year 2005, the "3 by 5" initiative, was conceived and implemented across the globe. The revised guideline for the use of 'ART in resource constrained settings' as suggested by the WHO is being followed in India. The free ART programme was launched on 1 April 2004, starting with eight tertiary level government hospitals in the six high prevalence states of Andhra Pradesh, Karnataka, Maharashtra, Tamil Nadu, Manipur, Nagaland and NCT of Delhi.[2]

The first line regimen, given as per NACO guidelines, for any patient requiring treatment after being diagnosed to have HIV is a combination of Zidovudine, Lamivudine and Nevirapine (ZLN). Zidovudine, Lamivudine and Efavirenz (ZLE) is used instead in patients who develop intolerance to nevirapine or in patients diagnosed to have concurrent tuberculosis.[3]

To monitor the patients on the ART regimens, the most commonly and repeatedly used parameters are the CD4 counts, hemoglobin levels and the body weight. There are evidences that the ART by itself will improve the CD4 counts,[3] hemoglobin level[4] and weight.[5] This study was undertaken to throw some light on how the two first line regimens, ZLN and ZLE, affected these prognostic parameters, as there are no comparative studies. By this study, probably, we can select the regimen that is appropriate to the patient depending on the pre-treatment levels of these three parameters.

MATERIALS AND METHODS

Methodology:

A retrospective observational study was designed and CD4 counts, hemoglobin and body weight were considered for analysis as they are commonly evaluated in the follow up of HIV patients on treatment as per NACO guidelines.[2] Ethical clearance was obtained (No: JJMMC/IEC-10/2011-12) from the local ethical committee and a permission was obtained from the Anti-Retroviral Therapy (ART) medical officer of the Chigateri Government District hospital, Davangere for data collection. Data of patients who had completed six months of treatment by the time the ethical clearance was given were collected.

Inclusion and exclusion criteria

Patients data was collected from July to September in the year 2012. Patients who were diagnosed to have HIV and are receiving zidovudine based HAART regimens; zidovudine, lamivudine and nevirapine (ZLN) or zidovudine, lamivudine and efavirenz (ZLE) were included in the study. Patient must have been on the same regimen for atleast six months and two readings of study parameters six months apart were the inclusion criteria for the study. Patients who have had a change in the regimen, for any reason, in the study period were excluded from the study.

Study groups and parameters assessed

Patients on ZLN regimen were included in group A. Patients who received ZLE were included in group B. The baseline CD4 counts, hemoglobin and weight of the eligible patients were recorded and the values of these parameters after six months were also recorded for comparison.

Statistical analysis

Online Graphpad software was used for statistical analysis of the study. Changes in the CD4 counts, hemoglobin and weight both before and after treatment in the individual groups were analyzed using the paired 't' test. Intergroup analysis was done using unpaired 't' test. A p value of 0.05 was considered significant.

RESULTS

A total of 500 patient records were taken out of which 356 patients were on zidovudine based regimens. We could find 339 patient records that could be included in our

study protocol of the 500 records checked as remaining did not meet the inclusion criteria. Of these 252 patients were on zidovudine, lamivudine and nevirapine regimen (Group A) and 87 were on zidovudine, lamivudine and efavirenz regimen (Group B). The male to female ratio of the patients who received the drug was as described in the Table 1.

Table 1: Number of male and female patients on Zidovudine based regimens

Regimen	Males	Females	Total
ZLN	125	127	252
ZLE	50	37	87

Z-zidovudine, L-lamivudine, N-nevirapine, E-efavirenz.

All the results are summarized in the table 2. The difference in the sample size for different parameters was due to the lack of complete data.

DISCUSSION

The three parameters chosen as variables in this study; the CD4 counts, hemoglobin levels and body weight, are preferred in most ART centres to evaluate the prognosis of the patients in their follow up. The CD4 counts can predict the patient's susceptibility to various opportunistic infections and thereby increasing mortality in People Living with HIV/AIDS (PLHA).[6] Hemoglobin can be a predictor of morbidity and rarely mortality that is independent of CD4 counts. A decrease in hemoglobin is one of the most common presentations of HIV.[3] The treatment with anti HIV drugs can also result in anemia. So to monitor the treatment or its adverse effects, hemoglobin becomes one of the important prognostic factors.[7] Change in the body weight of a HIV infected individual reflects change in rate of viral replication and it is also affected by opportunistic infections or malignant diseases.[5,8]

Apart from the viral load, the CD4 count is the most important predictor of mortality for a patient infected with HIV and is on treatment.[2] As viral load is not evaluated routinely in the ART centres but done at the centres of excellence,[9] the variable CD4 count was chosen as it is regarded as important predictor of mortality. It has been noted that the lower the counts of CD4, the harder it is to improve the count.[10] In accordance with the NACO guidelines the treatment with ART in the present study was initiated when CD4 counts dropped to 250.[9]

After the analysis of the data that we collected, we found that the number of people receiving ZLN was 252 and ZLE group had 87 patients. This implies that the first choice of ART according to the NACO guidelines is very

Table 2: Changes in the CD4 counts, hemoglobin and weight both before and after treatment

Parameter	Group	Treatment	Mean	Mean change	p	Group A v/s B p value
CD4 Counts (mm^3)	Group A (n=252)	Before	225.20	154.30	0.001	0.005
		After	379.50			
	Group B (n=87)	Before	191.80	91.20	0.001	
		After	283.00			
Hemoglobin (g%)	Group A (n=204)	Before	11.00	- 0.20	0.36	0.03
		After	10.80			
	Group B (n=77)	Before	10.00	0.90	0.001	
		After	10.90			
Body Weight (Kg)	Group A (n=252)	Before	51.88	1.42	0.001	0.21
		After	53.30			
	Group B (n=87)	Before	50.94	2.01	0.001	
		After	52.75			

Group A-ZLN regimen, Group B-ZLE regimen, $p < 0.05$ is statistically significant.

well tolerated and the second line is rarely required. Both the regimens, with six months of treatment, were associated with an increase in the mean CD4 counts with a p value of 0.001 but the mean increase was better with the nevirapine based regimen. This shows that the nevirapine based regimen is better in improving CD4 counts when compared with efavirenz group (p = 0.005) if the person tolerates the regimen or doesn't have any tuberculosis as it interacts with rifampicin in the anti-tubercular regimen. In these exceptional cases efavirenz is substituted for nevirapine. A meta-analysis has shown that the efavirenz based regimens are better in patients with a co-infection with HIV and Tb. The researchers have also opined that when efavirenz cannot be substituted instead of nevirapine, a nevirapine based regimen is also an effective alternative in patients receiving both ATT and ART.[11] The analysis of our data shows that when it comes to CD4 counts ZLE also improves the counts significantly implying that though ZLN regimen is better ZLE is also efficient.

Harris RJ, et al reported from their study that anemia at baseline in a HIV patient was independently associated with higher mortality. According to them baseline anemia continued to be a predictor of mortality and to a lesser extent progression to AIDS too.[12] Amanda Mocroft, Ole Kirk et al in a study conducted in Europe that included 6725 HIV patients found out that 1 g% decrease in the hemoglobin increased the hazard of death by 57% (relative hazard), a drop in 50% of the CD4 counts increased the hazard by 51%. Also the drugs given to treat HIV, especially zidovudine has a tendency to decrease the hemoglobin levels.[13] This indicates that hemoglobin is a more important prognostic factor in a patient with HIV not only to see the prognosis of the patient but also to monitor treatment related adverse events.[12]

In our data, the average hemoglobin in the group A was 11.0g% and after six months of treatment it was 10.80g%. There was a decrease of 0.2g% in the mean hemoglobin level. In the patients who received ZLE, the mean hemoglobin improved by 0.9g%. Among all the drugs in the two regimens only zidovudine is the drug that is known to cause anemia.[14-16] The drug being the common factor in both the regimens the reason for the hemoglobin levels to decrease in group A is unexplained. If nevirapine, the only variable among the two groups, has any role in this has to be ascertained. So a controlled study with adequate power can substantiate if efavirenz based regimen improves hemoglobin better than nevirapine based regimens.

In a brief report published by Society of Infectious Diseases of America in the year 2000, the authors have found that the wasting of >10% was seen in 58% of patients and 50% of them were on HAART.[10] In patients with HIV infection, loss of metabolically active tissue results in an increase in mortality, accelerated disease progression, impairment of strength and functional status. Although a loss of 10% body weight in 3 months has been considered for suspicion of HIV, even a loss of 5% has been associated with increasing morbidity and mortality[17] and hence AIDS is also called the 'slim's disease'.

In our study population, the weight in both groups improved. In group A, the improvement was 1.42 Kg and in group B it was 2.01 after six months of treatment. Before initiation of treatment the groups showed a mean difference of 0.94 Kg where group A had better average weight. After six months of treatment the mean difference in weight was 0.5 Kg. This difference was due to the better improvement in the ZLE group (0.69 Kg better than group B). The reason for better improvement in group B is not known. As there was no significant statistical difference in the improvement of body weight between the two groups, the choice of the regimen opted need not be changed when body weight is a factor under consideration.

The CD4 counts improved with both the regimens significantly but improvement in ZLN group was better. Mean hemoglobin decreased in the ZLN group with treatment whereas it improved in the ZLE group. Both the regimens were effective in improving the weight significantly. When the CD4 counts and the body weight are the factors under consideration, either of the regimen can be opted for the patient as per the NACO guidelines. If the patient is anemic, probably ZLE can be preferred. A study with a calculated sample size in both the groups will help in ascertaining the relationship between hemoglobin and the two regimens.

Limitations of the study

One important confounder in our study is the unavailability of the details of nutritional supplementation given to the patients that might have had a big impact on the parameters. The other factor is sample size discrepancy between the two groups. Also 41 patients who were on ZLE had tuberculosis and so they were also receiving anti-tubercular treatment. A separate study, in the same set up, showed that there was a better improvement in weight compared to those who were not infected with tuberculosis.[18] If the documentation of adverse effects was proper, then their influence on the outcome could have been analyzed.

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REFERENCES

1. WHO [Internet]. Switzerland: Global situation and trends. [cited on 2013 Nov 4]. Available from: www.who.int/gho/hiv/en/.
2. Pokala N, Dixit R, Manubhai PM, Vijayala K. Adverse drug reactions with second line antiretroviral drug regimen. Asian J Pharm Clin Res 2014;7:75-9.
3. Ministry of health and family welfare [Internet]. Government of India; [updated 2007 May; cited 2014 April 18]. Anti-retroviral therapy guidelines for HIV infected adults and adolescents including post-exposure prophylaxis. Available from: http://apps.who.int/medicinedocs/documents/s18021en/s18021en.pdf.
4. Sharma SK. Zidovudine induced anaemia in HIV/AIDS. Indian J Med Res 2010;132: 359-61.
5. Grinspoon S, Mulligan K. Weight loss and wasting in patients infected with human immunodeficiency virus. Clinical Infectious Diseases 2003;36:S69-S78.
6. Wendland T, Furrer H, Vernazza PL, Frutig K, Christen A, Matter L, et al. HAART in HIV infected patients: restoration of antigen specific CD4 memory T-cell reconstitution, whereas improvement in delayed type hypersensitivity is related to a decrease in viraemia. AIDS 1999;13:1857-62.
7. Takuva S, Maskew M, Brennan AT, Sanne I, MacPhail AP, Fox MP. Anemia among HIV-infected patients initiating antiretroviral therapy in South Africa: improvement in hemoglobin regardless of degree of immunosuppression and the initiating ART regimen. Journal of Tropical Medicine 2013; doi:10.1155/2013/162950.
8. Brechtl JR, Breitbart W, Galietta M, Krivo S, Rosenfeld B. The use of highly active antiretroviral therapy (HAART) in patients with advanced HIV infection: impact on medical, palliative care, and quality of life outcomes. Journal of Pain and Symptom Management 2001;21:41-51.
9. National AIDS control organization, [Internet]. Government of India; [updated 2012 July; cited 2014 April 18]. Operational Guidelines for ART services. Available from: http://www.naco.gov.in/upload/Publication/Treatment%20Care%20and%20support/Operational%20guidelines%20for%20ART%20services.pdf.
10. Wanke C. Treatment of tuberculosis in HIV infected persons in the era of highly active antiretroviral therapy. AIDS 2003;17:S112-4.
11. Jiang H, Zhang M, Chen H, Yang Y, Deng M, Ruan B. Nevirapine versus efavirenz for patients co-infected with HIV and tuberculosis: a systematic review and meta-analysis. International Journal of Infectious diseases 2014;25:130-5.

12. Harris RJ, Sterne JA, Abqrall S, Dabis F, Harris RJ, Sterne JA, Abqrall S, Dabis F, Reiss P, Saaq M et al. Prognostic importance of anaemia in HIV type – 1 infected patients starting antiretroviral therapy: collaborative analysis of prospective cohort studies. Antivir Ther 2008;13:959-67.

13. Mocroft A, Kirk O, Barton SE, Dietrich M, Proenca R, Colebunders R, et al. Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients from across Europe. AIDS 1999;13:943-50.

14. Tripathi KD. Essentials of medical pharmacology. 7th ed. New Delhi: Jaypee; 2013. p.806-9.

15. Sharma HL, Sharma KK. Principles of pharmacology. 2nd ed. Hyderabad: Paras; 2011.p.789-92.

16. Flexner C. Antiretroviral agents and treatment of HIV infection. In: Laurence LB, editor. Goodman and gilman's the pharmacological basis of therapeutics. 12th ed. New Delhi: McGraw Hill; 2011.p.1632-43.

17. Tang AM, Forester J, Speigelman D, Knox TA, Tchetgen E, Gorbach SL. Weight loss and survival in HIV-positive patients in the era of highly active anti-retroviral therapy. J Acquir Immune Defic Syndro 2002;31:230-6.

18. Dinakar KR, Sanji N, Aggarwal V, Reshma SR, Somashekar HS, Keerthisagar J. Changes in the CD4 counts, hemoglobin and weight in patients with HIV alone and HIV- TB co-infection. Asian J Pharm and Clin Res 2014;7:S35-S38.

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