

Treatment Outcome of Second Line Anti-retroviral Therapy in HIV Positive Patients Over One Year Period

Dharmendra Kumar Jha¹, Umesh Kumar Ojha², Anshu Kumar Jha³

ABSTRACT

Introduction: In India, the second line regimen has still not been studied extensively when compared to its first line counterpart. In our study we accessed the clinical, virological and immunological effectiveness and treatment outcome over the one year of follow-up in our patients who were switched to the second line.

Material and Methods: It was a prospective, observational study which included patients who were switched to second line ART from Jan2017 - Dec2017 at ART Centre of PMCH Dhanbad. Clinico-demographic details, symptoms, adverse drug reactions (ADRs), second line ART regimens, CD4 count, and plasma viral load (PVL) were recorded. Monthly follow-up was done. The data was analyzed by *t*-test, *z*-test, and Fisher-exact test.

Results: Out of 100 patients, 70 received regimen I [zidovudine (ZDV) + lamivudine (3TC) + tenofovir (TDF) + boosted lopinavir (LPV/r)] and 30 received regimen II [3TC + TDF + LPV/r]. Significant ($P < 0.0001$) increase in mean body weight, marked reduction in viral load and those patients who were categorized in the WHO stage III/IV was observed at 12 months of second line ART. Significant improvement in immunity was observed clinically with an increase in mean CD4 count. Viral suppression (PVL < 400 copies/ml) was observed in 87 patients ($P < 0.0001$). A total of 74 ADRs were observed in 53 patients.

Conclusion: Treatment outcome of second line ART was good as patients improved both clinically and improvement in laboratory data was also observed. Anemia was the most common ADR observed in the study.

Keywords: ART, Viral Load, ADR.

free of cost. The second line ART regimens comprised of zidovudine (ZDV), lamivudine (3TC), tenofovir (TDF), and boosted lopinavir/ritonavir (LPV/r) have been introduced recently in a phase wise manner at various centers.⁷ The criteria to switch on second line ART are clinical and/or immunological and/or virologic failure in a patient who had received 6 months or more of standard first-line ART, i) if CD4 declines to pre-ART values, ii) if CD4 drop to less than 50% of peak on-treatment value, iii) failure to achieve CD4 greater than 100 c/mm³ (immunologic failure), iv) develop a new WHO stage III/IV AIDS-defining illness (clinical failure), v) those with HIV RNA 10,000 c/ml or greater (virological failure).⁷ The second line regimen as compared to its counterpart has been less studied. Without resistance testing and 6 monthly virological monitoring, the consequences of second line therapy outcomes are unclear. Thus, it is very important to assess the clinical, virological, and immunological effectiveness and treatment outcome of those patients who were switched to second line therapy from their first line ART due to various reasons. In our study we accessed the clinical, virological and immunological effectiveness and treatment outcome over the one year of follow-up in our patients who were switched to the second line.

MATERIAL AND METHODS

This was a longitudinal, prospective, observational, single center study conducted at ART center of PMCH Dhanbad. The study was approved by Institutional Ethics Committee (IEC). Inclusion criteria were – i) HIV positive patients of more than 18 year, ii) must have been switched to second line ART from January 2017 to December 2017 at ART center. However, pregnant women were excluded. Informed consent was obtained from all patients.

INTRODUCTION

Today AIDS has stepped into its third decade with several treatment experienced patients across the world. However, due to many factors like non-compliance with the regimen, mutations by the virus has led to resistant strains coming up.¹ The advent of highly active antiretroviral therapy (HAART) has been a boon for human immunodeficiency virus (HIV) infected patients by reducing morbidity and extending lifespan.² There have been increasing reports of MRD (multi-drug resistant) virus in treatment-experienced patients.³ This has been a major contributory cause to first line antiretroviral therapy (ART) failure which forces a physician to switch over to the second line, protease inhibitor (PI)-based regimen.⁴ India ranks third among the countries having the greatest number of PLHIV (People Living with HIV) and HIV related deaths in the world.^{5,6} In India, under the banner of National AIDS Control Organization (NACO) various ART centers have been opened where these drugs are provided

¹Associate Professor, Department of Medicine, Patliputra Medical College and Hospital, Dhanbad, Jharkhand, ²Professor, Department of Medicine, Patliputra Medical College and Hospital, Dhanbad, Jharkhand, ³Postgraduate, Department of Medicine, Assam Medical College and Hospital, Dibrugarh, Assam, India

Corresponding author: Dr. Anshu Kumar Jha, Room no. 47, PG Boy's Hostel, Assam Medical College, Dibrugarh, Assam, 786002, India

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| Parameters | Patients on Regimen I (70) | Patients on Regimen II (30) |
|---------------------------|----------------------------|-----------------------------|
| Age (years) | 37 ± 3.4 | 40 ± 5.6 |
| Weight (kgs) | 48 ± 3.5 | 46 ± 7.1 |
| CD4 count | 147 ± 5.1 | 115 ± 4.9 |
| Peripheral Viral Load | 254784 ± 25654.6 | 205421 ± 11847.2 |
| Opportunistic infections- | | |
| i). Tuberculosis | 14 (100%) | 10 (100%) |
| ii). Oral Candidiasis | 10 (71.4%) | 08 (36.6%) |
| iii). Herpes | 03 (21.4%) | 00 |
| | 01 (7.14%) | 02 (20.0%) |

Table-1:

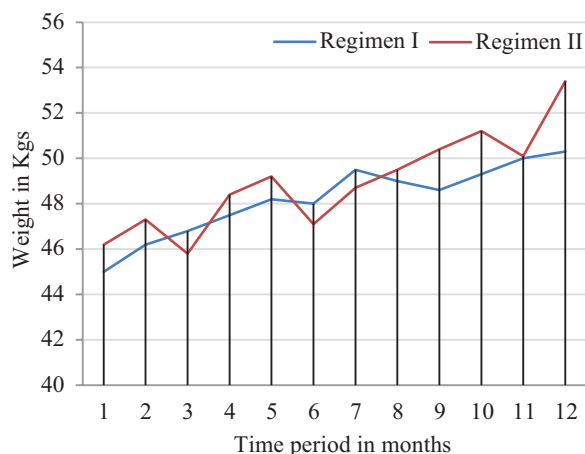


Figure-1: Co-relation between weight gain with respect to regimen 1 and 2 over the whole period of the study

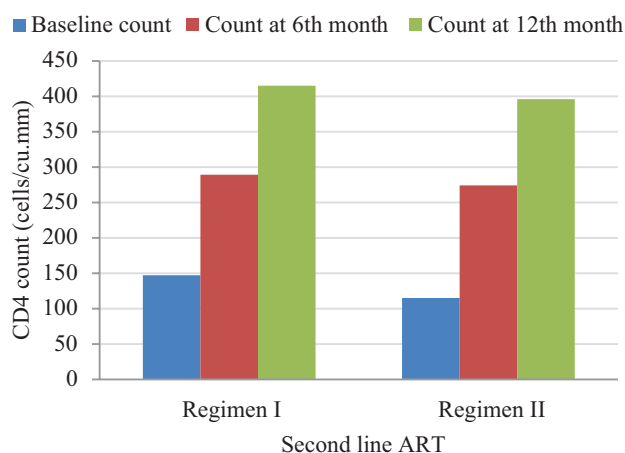


Figure-2: CD4 cell count at baseline, at 6th month and 12th month

The baseline data of the patients was recorded. Every patient was followed-up monthly for clinical assessment (body weight, WHO stage, opportunistic infections) and adverse drug reaction (ADR) till the completion of 1 year of second line treatment. CD4 count was monitored at baseline, 6th month and 12th months and plasma viral load (PVL) was tested at baseline and 6th months after switching to second line ART regimen. However, patients who failed to show virologic suppression (<400 copies/ml) at 6 months, PVL was repeated at 12 months. Patients were sent to Integrated Counselling and Testing Center (ICTC) at each visit. Adherence to second line therapy was assessed by pill count.

STATISTICAL ANALYSIS

The data was recorded in Microsoft Excel Worksheet and

analyzed by z-test, t-test, and Fisher's exact test.

RESULTS

A total of 100 patients were taken into study of which 75 were male and 25 were female. 70 were treated on Regimen I [zidovudine (ZDV) + lamivudine (3TC) + tenofovir (TDF) + boosted lopinavir (LPV/r)] and 30 received regimen II [3TC + TDF + LPV/r]. Mean age of the patients was 36.7 ± 8.7 yrs. The most common reason for switching over to 2nd line regimen was immunological failure associated with virological failure (85) followed by all three failure (15). The base line CD4 count was compared between the groups receiving regimen I and II (Table 1). As expected the most common opportunistic infection was tuberculosis caused by *Mycobacterium tuberculosis* (18). It was followed by oral candidiasis (03) and herpes (03).

Clinical assessment of the results over improvement in the patients on second line ART (both regimen I and II) showed a significant increase in the body weight of patients at 6th and 12th month of treatment ($P < 0.001$ and $P < 0.0001$). However, patients on regimen II showed a better clinical improvement as compared to patients on regimen I in terms of weight gain ($P < 0.01$) [Figure 1]. Treatment of opportunistic infection was successful in 13 (54.16%) patients at 6 months and rest 11 (45.8%) got cured at 12 months. Immunological assessment was done by comparing the CD4 count level at 6th month and 12th month with the base line in both the groups [Figure 2]. Results were statistically significant ($P < 0.001$).

Virologic suppression was accessed by looking at mean PVL at 6 months treatment with both second line ART regimens ($P < 0.0001$). Out of 100 patients, 55 patients achieved virological suppression (PVL < 400 copies/ml) at 6 months and 45 patients at 12 months. Further analysis showed that in regimen I, 45 patients achieved virological suppression at 6 months and rest 25 at 12 months whereas in regimen II, 10 patients achieved virological suppression at 6 months and rest 20 at 12 months.

Total number of adverse drug reactions (ADRs) was counted to be 74 in 53 patients. Most common was anemia which was seen in 33 patients followed by rash seen in 10 patients. Lactic acidosis was observed in 5 patients and 5 patients presented with myopathy. Rest 21 ADRs were overlapping with more than one in a patient.

The pill count showed that most patients in both groups (94% and 95%) on second line ART were adherent to the treatment with more than 95% adherence. The number of tablets to be consumed by each patient per day in regimen I and II was 7

and 5, respectively.

DISCUSSION

Almost after 35 yrs of discovery of HIV today many patients are on ART for lifelong period. With various factors playing role today we also have to deal with drug resistance and treatment failure. As the number of patients on ART increases there will surely be an increase in patients switching to second line therapy. In our study we show an analysis describing the outcomes of 100 patients on second line LPV/r-based ART regimens for 12 months treated at ART center of PMCH Dhanbad, Jharkhand state, India. After 12 months of follow-up on second line regimens, all 100 patients remained on treatment with no deaths or drop outs. A strong immune reconstitution with clinical improvement (body weight and Opportunistic infection) was observed at 12 months of follow-up on second line ART regimens. The immunologic and virologic data supports our observation that the patients were indeed adhering well (>95%) despite high pill count (7 and 5) and difficulties to store LPV/r.

Out of 100 patients, 48 had clinical failure while 68 had immunological and 79 had virological failure at the start of therapy. Despite this 54 patients were asymptomatic at the time of enrolment pointing to the fact that clinical failure manifest at late stage and is a poor indicator to diagnose first line treatment failure.

Our study showed that the most common age group was 31-49 years. Secondly, the mean age of patients in our study was higher (36.7 ± 8.7 years) as compared to studies documented at Thailand, Médecins Sans Frontières (MSF) countries and South Africa (35yrs).^{8,9,10} There were more men (78%) than women in our study indicating high HIV prevalence among males. However, national data shows that 53% of the total HIV infected patients are men, which is lower than our finding.¹¹

At the time of initiation of second line ART regimen, the CD4 count was lower and PVL was higher in our study. When compared to similar studies done at Thailand⁸ and South Africa^{10,12} our study showed a lower CD4 count and a higher PVL at the beginning of therapy. This finding points out the inefficiency of our center to detect first line treatment failure early thus delaying the start of second line treatment. This delay may be due to limited resources and predefined indicators to detect the treatment failure. The National AIDS Control Organization (NACO) guidelines defines virological failure with PVL >10,000 copies/ml, while this is only >1000 copies/ml in Thailand and South Africa^{8,10,12}. Due to this delay patients have immunological deterioration thus ending up suffering from various life threatening opportunistic infections. As suggested by AJose et al., patient should be switched to second line ART as soon as the PVL is more than 400 copies/ml.¹³ There was a steady increase in the CD4 level throughout the study. Median increase in CD4 count at 12 months treatment was higher as compared to similar studies done at Cambodia and MSF countries (284 vs 135 cells/mm³).^{9,14} Thus, our study observed better immunological outcome.

The ADR documented maximum in our study was anemia followed by rash. Anemia was more commonly seen in regimen I which could be explained by the use of zidovudine in the regimen. Similar findings were observed in a study done by Jha et al. where maximum number of anemia as an ADR was attributed to zidovudine.¹⁵ Rash, lactic acidosis and myopathy were also observed which were known adverse effects of second line ART drugs.

So, finally looking at the data collected from a 12 month follow up we could satisfactorily establish the early treatment outcome of second line ART. The success rate of second line ART regimen was 82%, which is quite satisfactory and comparable with other second line ART regimens. Also, no major difference was seen when the efficacy of both the regimen were compared for achieving viral suppression. Improvement in body weight was more in regimen I but increase in CD4 count was more in regimen II. Thus, addition of zidovudine to second line regimen (3TC + TDF + LPV/r) provides no additional benefit in terms of efficacy and on the other hand increases the risk of anemia and pill burden. So, removal of zidovudine from the regimen shall cut the cost and reduce the financial burden over the government body. Also, the NACO should consider revising the treatment failure criteria which are much strict in countries like Thailand and South Africa leading to early initiation of the second line regimen.

CONCLUSION

Finally, we state that there are obvious clinical, immunological and virological improvement in the patient who are switched over to second line ART when followed up over a period of 1 year. But further studies are required to see for how long the effect persists.

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