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***Research***

# Study on Highly Active Anti- Retroviral Therapy: prescription pattern and side effects

**Sujata Sapkota[1)], Rajani Shakya[1)], Basudev Pandey[2)]**

[1)]Department of Pharmacy, Kathmandu University, Kavre, Nepal
[2)]ART Centre, SukraRaj Tropical and Infectious Disease Hospital, Teku, Kathmandu, Nepal

**Abstract**

Since the introduction of Highly Active Anti Retroviral therapy (HAART) by World Health Organization in 1996, it has been the employed method of drug use in HIV management. Involvement of multiple drugs in the regimen, has also invited multiple complications and side effects is one of them. High chances of occurrence of side effects has called for the need of proper identification and therapy management tools for each HAART user and has highlighted the importance of individualized drug therapy. The aim of the study the prescription pattern of the HAART regimen; frequency of regimen change and its major causes; and the side- effects from HAART. The study was conducted in the ART Clinic of SukraRaj Tropical & Infectious Disease Hospital, Teku. 109 patients, who came to the clinic to refill their prescription, were interviewed by the researcher. After interview, medication file of each patient was reviewed to study the prescribed drug regimen, drug changes and identified reasons for the drug change (as identified by the physicians and recorded in patient medication file); reported side effect experience and laboratory reports were analyzed to study the effect of the HAART regimen on hemoglobin and Alanine Aminotransferase enzyme. The study revealed that the most prescribed HAART regimen constituted a combination of Zidovudine, Lamivudine and Nevirapine. 52% of the patients reported having experienced side effects from HAART. 23.85% patients had to have their initial regimen changed because of drug toxicity. Nausea (15.6%), vertigo (14.7%), decreased hemoglobin (11.9%), skin rash/ allergy (9.2%) were the major side effects experience reported by the patients. In addition to some side effects like nausea, vertigo etc; decrease in the level of hemoglobin after the initiation of HAART was evident. Decrease in Zidovudine containing regimen, during the regimen change was apparent and was mostly related to its hemoglobin lowering activity.

*Key words:* Highly Active Anti Retroviral Therapy (HAART), People Living with HIV/AIDS (PLHA), Prescription pattern, Side effects

## Introduction

Management of HIV/ AIDS involves the use of Anti Retro -Viral (ARV) Agents. [1,2,3 ] ARV drugs inhibit the replication of HIV.[4] Although they cannot cure HIV/ AIDS, the drugs have succeeded to a larger extent in reducing the morbidity and mortality, in addition to improving the quality of life of people with HIV/ AIDS [3,5]. The drugs help the immune system to stay healthy and able to fight infection. To overcome the problem of resistance arising from the use of 1 or 2 ARV drugs and to strengthen the effectiveness of therapy, World Health Organization (WHO) in 1996 introduced Highly Active Anti-Retroviral Therapy (HAART), which incorporated the use of 3 or more ARV drugs in the ART regimen. [2,6,7] Since then, HAART has been the employed method of drug use in HIV management all over the world.

Along with various difficulties associated with the therapy, viz. multi- drug regimen, drug interactions etc, side effects has been recognized as one of the major problems. Studies have shown that side effects occur in almost 50% of the HAART consumers. The side effects of ARV therapy has also been found to range from merely bothersome effects to effects that are potentially dangerous, and the side-effects have been found to vary depending on the drug regimen. GI intolerance, Renal, Hepatic and Hematological side effects are reportedly the most common. [2,8 ].

**Corresponding Author:*
Sujata Sapkota, Department of Pharmacy, Kathmandu University. E-mail: sapkota_sujata@hotmail.com

The Government of Nepal launched the first free ARV treatment & distribution program in 2004. Since then many People Living with HIV/AIDS (PLHA) have been receiving the therapy in the country. With increase prescriptions being written, there is an increased need for the assessment of various aspects associated with the therapy, and their evaluation.

## Methods

The research is an interview based, non- interventional, observational, cross comparative study. The research methodology involved: patient interview and medication file review. Based on semi structured questionnaire prepared by the researcher, the patients were asked to report whether they experienced any kind of side effect after starting HAART and what kind. For the analysis purpose, side effects were categorized as: Minor side effects and Major side effects, as follows:

**Table 1.** Basis for categorization of the reported side effects

| Experienced Side Effects? | Category | Explanation |
|---|---|---|
| Yes | Minor | The patient reported experiencing side effects like nausea, vomiting, GI upset etc which subsided over a period of time |
| | Major | The side effects that ultimately led to regimen change |
| No | | The patient did not report of having expierienced any difficulty with his ARV medications |

Patients were also asked if they voluntarily stopped taking their medications because of the side- effects, and if they did have a prior knowledge regarding the possibility of side effects with the therapy.

Minor side effects were determined based on the patient self reports.

Medication file review was conducted for each patient to record the prescribed regimen, regimen change and the reasons for regimen change (as reported by treating physician/s for the individual patient and recorded in the patient medication file). Lab records of hemoglobin and Alanine Aminotransferase enzyme (ALT) before and 15 days after therapy for 69 and 49 patients respectively were also studied, to analyze whether the hemoglobin lowering effect and effect on liver enzymes due to HAART were significant at $p<0.05$ (T- test).

The study was conducted in the ART Clinic of SukraRaj Tropical and Infectious Disease Hospital, Teku, Kathmandu, Nepal. The sample population constituted of 109 PLHA, who had been consuming HAART for not less than 3 months, who came in to the clinic for the refill of their prescriptions. Pregnant women, patients less than 15 years of age and in- patients admitted in the hospital ward were not included in the study.

Ethical permission for the conduction of research was taken from Nepal Health Research Council and other legal formalities like informing the participant regarding the research and the researcher, taking consent (both verbal and written) from each patient were conducted before the interview.

## Results

Of the total PLHA interviewed, 64.22% were males and 35.78% were females. The interviewed sample population incorporated PLHA of the age group 22- 58 years. Majority of the population (93.58%) were under the age group 22- 49 years.

Prescription pattern:

*Frequently prescribed initial HAART regimen*

The most frequently prescribed initial HAART regimen constituted a combination of Zidovudine (ZDV) 300mg, Lamivudine (3TC) 150 mg and Nevirapine (NVP) 200 mg. The drug, for initial 14 days was prescribed as ZDV/ 3TC to be taken twice a day (BD), and NVP to be taken once daily. Then after, NVP was also continued on twice daily basis. Second most frequently prescribed regimen constituted a combination of ZDV 300mg, 3TC 150 mg, the combination to be taken BD along with Efavirenz (EFV) (600mg or 800 mg) which was to be taken at bed time. Combination of Stavudine (d4T) 30 mg, 3TC 150 mg and NVP 200 mg was preferred when ZDV did not become the initial choice. The most prescribed HAART regimens and their occurrence percentage is shown in the figure 1:

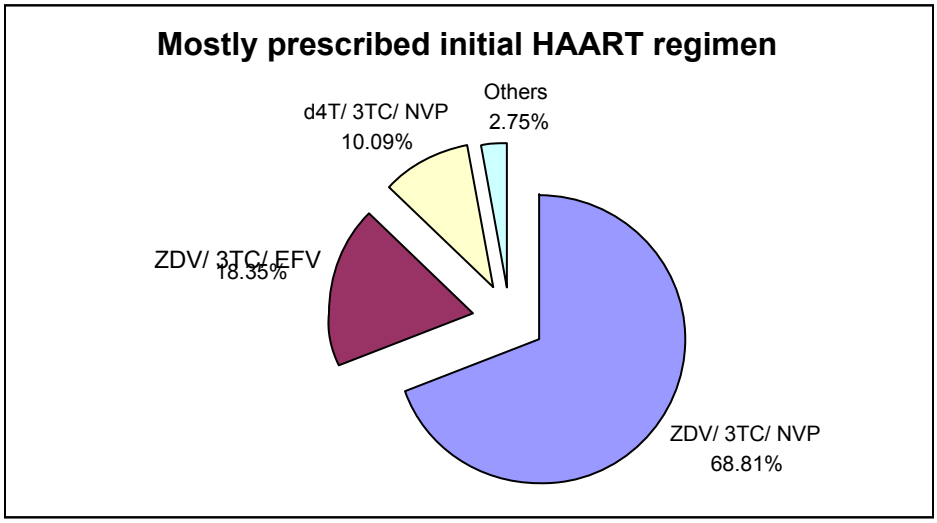


Figure 1. Initial HAART regimen prescription pattern

Figure 1. Initial HAART regimen prescribing pattern

*Regimen change*

Out of the 109 PLHA receiving HAART, 38 (i.e. 34. 86%) underwent ART regimen change. Whereas, drug toxicity was the major reason for change (as reported from patient medication file review); few patients were also found to have changed their regimen so that the number of pills to be consumed was reduced. The regimen so chosen constituted a fixed dose combination of d4T/ 3TC/ NVP. Table below illustrates the major reasons for the change of initially prescribed regimen along with the percentage:

**Table 2.** Major reasons for change in initial HAART regimen prescribed

| **Reasons for regimen change** | **Number of patients** | **% out of total regimen changed** (n=38) |
|---|---|---|
| Drug Toxicity/ Side Effects | 26 | 68.42% |
| Newly diagnosed TB , Addition or Withdrawal of TB drugs | 7 | 18.42% |
| Miscellaneous (treatment failure / voluntary drug change/ unspecified reasons) | 5 | 13.16% |

*Prescription pattern after regimen change*

Whereas, the mostly prescribed initial regimen combination (ZDV/ 3TC/ NVP) still held the highest prescription percentage, the prescription percentage declined from 68.81 to 44. It was also observed that there was significant increase in the percentage prescription of the combination d4T/ 3TC/ NVP (from 10.09 to 24.8).

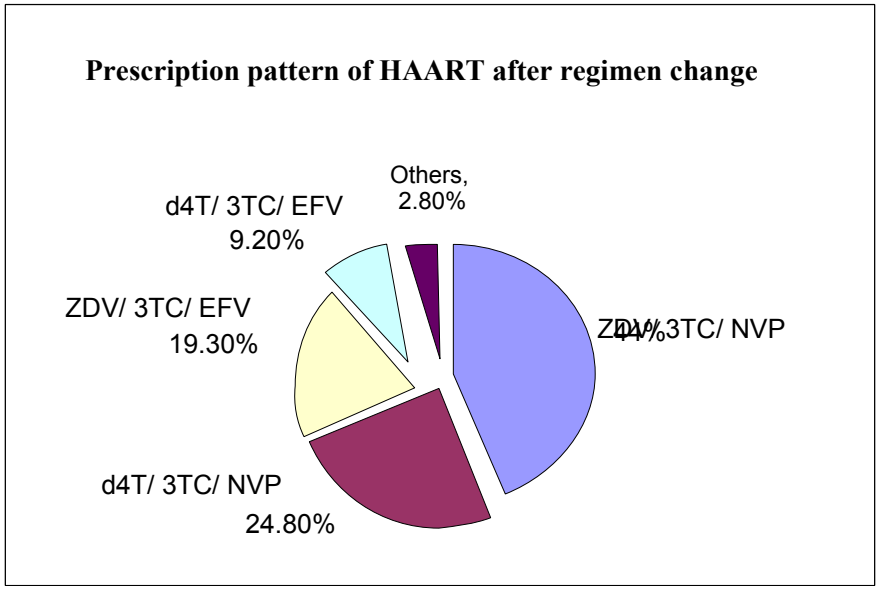


**Figure 2.** HAART regimen prescription pattern after regimen change

Side Effects

*Prevalence of side effects amongst HAART users*

Among the sample population interviewed, more than half (52.29%) of the total patients reported to have experienced side effects from HAART.

Based on the retrospective analysis of the patient medication file, it was found that 23.85% (26 out of 109) of the patients had to have their initial regimen changed because of drug toxicity/ side effects (categorized as major side effects). Thirty one patients (i.e. 28.44%), however, reported having minor difficulties, mostly during earlier days of their therapy.

**Table 3.** Categorization of the population based on severity of side effects

| | Category | No. of patients | % |
|---|---|---|---|
| NO | No side effects | 52 | 47.71% |
| | Minor side effects | 31 | 28.44% |
| YES | Major side effects | 26 | 23.85% |
| | **Total** | **109** | **100** |

Majority of the patients reported having experienced a diverse set of adverse effects. Nausea, vertigo, lowered hemoglobin (Hb), skin rashes were the side effects mostly reported. The difficulties that were

reported by the patients as side effects during interview are listed below along with the percentage of occurrence:

**Table 4.** Side effects from HAART as reported by the interviewed population

| Side Effects reported | Occurrence Rate | | |
|---|---|---|---|
| | No. of PLHA | % (out of total population, 109) | % (out of those who claimed having experienced side effects from HAART, 57) |
| Nausea | 17 | 15.6 | 29.8 |
| Vertigo | 16 | 14.7 | 28.1 |
| Decreased Hb | 13 | 11.9 | 22.8 |
| Skin rash/ allergy | 10 | 9.2 | 17.5 |
| Anorexia | 9 | 8.3 | 15.8 |
| Vomiting | 9 | 8.3 | 15.8 |
| Dizziness | 5 | 4.6 | 8.8 |
| Jaundice | 3 | 2.8 | 5.3 |
| Restlessness | 2 | 1.8 | 3.5 |
| Weakness | 2 | 1.8 | 3.5 |
| Constipation | 2 | 1.8 | 3.5 |
| Hallucination | 1 | 0.9 | 1.8 |
| Fever | 1 | 0.9 | 1.8 |
| Insomnia | 1 | 0.9 | 1.8 |

None of the patient reported having stopped their drug voluntarily after the occurrence of side effects. 66 out of 109 reported that they were aware about the possibility of side effects from ARV therapy prior to start of the therapy.

### *Alterations in hemoglobin & ALT level due to HAART use*

#### ALT Status

32 out of 49 patients showed increase in ALT level, 15 days after initiation of ART. The increase in ALT was found significant when tested for [ALT (before therapy) – ALT (15 days after therapy)] in 49 patients (T- value = -2.30; P- value= 0.013, n= 49).

#### Hemoglobin Status

Analysis based on the lab reports and patient record file of patients where both pre and post Hemoglobin count was recorded, showed a decrease in hemoglobin level 15 days after HAART (T-Value = 1.88; P-Value = 0.032, n= 69). Fall in hemoglobin level was found in 40 patients (out of 69). The decrease ranged from 0.1 gm/dl to a decrease of 6.3 gm/ dl.

## Discussion

The cumulative toxicity of the available ARV agents has been one of the major concerns for the success of HAART. Side effects of HAART have been found to range from minor effects to potentially deadly.[2] However, since side effects categorization, done in the study, is based moreover on patient self report and the retrospective analysis of the reasons recorded, more complicated side effects, or the anticipated long term complications leading to the decision in regimen, might have been missed out, either because they were not recorded in the file or the patients were not aware of the potential complication. Their report (of

minor experience) is moreover based on their experience with the therapy. As found elsewhere, the study has also indicated an occurrence of side effects in more than 50% of the patient population.[9]

ZDV and 3TC, the drugs of Nucleoside Reverse Transcriptase Inhibitor (NRTI) group, formed the two most frequently prescribed drugs in the HAART regimen, used in majority of the cases with a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) (EFV or NVP). The prescribing pattern is found consistent with the National Guidelines.[6] However, the patients had to be shifted to other regimens due to different reasons. There was decrease in ZDV and NVP containing formulations after the change in regimen initially prescribed. This decrease as seen is mostly associated with the side effects which in a long run could result in more severe toxic effects, viz. anemia (primarily due to ZDV) and liver toxicity (primarily with NVP). Anemia, neutropenia and bone marrow suppression has been identified as the major toxicities of ZDV, and other NRTIs.[2,3,6] Similarly, NNRTIs have mostly been linked with side effects such as rash, increase ALT etc. Hepatic toxicity has been reported particularly with NVP.[6]

Besides the increase in ZDV and NVP constituting regimen, an increase in EFV containing regimen after the regimen change was also reported. Increase in EFV constituting regimen probably goes to the fact that EFV was a preferred choice when the patient was diagnosed with tuberculosis and had to have anti- TB regimen (especially that containing Rifampicin) along with HAART. Rifampicin has been shown to decrease the serum concentration of NVP by 20-55%. Besides, the common toxicities of NVP—skin rash and hepatitis—overlap common toxicities of some first-line anti-tuberculosis drugs.[10] Although, not conclusive, the collected experience has been stated as sufficient to make NVP an alternative for patients unable to take EFV and who do not have access to rifabutin. [10]

Statistical test conducted for the analysis of the effect of HAART on Hemoglobin and ALT profile before therapy and 15 days after initiation of therapy has shown a decrease in Hemoglobin and an increase in ALT after HAART, thus ensuring the necessity for the tests conducted on regular intervals to evaluate liver enzyme and blood profile etc. Guidelines have emphasized on the measurement of Complete blood count, Hemoglobin (%), Urea, Creatinine, ALT, VDRL, HBsAg, Anti HCV screening for Tuberculosis before initiating HAART. Tests to be repeated two weeks post therapy include: complete blood count, Hemoglobin (%), Urea, Creatinine, ALT.[6] based on this guideline necessary tests are carried out and only after two weeks, decision as to continuation/ discontinuation or change of regimen is advised.

Despite the side effects the patients have experienced from HAART, none reported having voluntarily stopped taking their medicines. About 2/3$^{rd}$ of the population also reported that they were aware regarding the possibilities of side effects from HAART. Pre ART counseling provided to each patient before they were given their first dose of HAART have helped the patient to cope up with difficulties arising from HAART, and guided them to seek professional consultation for managing the difficulties, rather than making a voluntary effort.

**Conclusion**

The most prescribed HAART regimen constituted a combination of ZDV/ 3TC/ NVP. 52% of the patients reported having experienced side effects from HAART. 23.85% patients had to have their initial regimen changed because of toxicity. 60.55% reported that they were aware about the possibility of side effects prior to start of therapy. None reported having voluntarily stopped any drug because of side effects.

Nausea (15.6%), Vertigo (14.7%), Decreased hemoglobin (11.9%), Skin rash/ allergy (9.2%), Anorexia (8.3%), Vomiting (8.3%), Dizziness (4.6%) etc were the major side effects experience reported by the patients. Increase in ALT level and decrease in Hemoglobin level were significant after therapy.

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