ADVERSE EFFECT PROFILE OF ANTIRETROVIRAL DRUGS IN THE INITIAL THREE MONTHS OF THERAPY
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ABSTRACT

BACKGROUND
HIV disease is becoming increasingly prevalent. With ART being available in government ART centres and also drugs prices getting cheaper, most HIV patients receive ART. Success of ART treatment depends on patient compliance and major factor interfering with compliance is drugs toxicities. Adverse effects often trivial earlier are the major cause of patient drop out.

Accordingly, we studied ART toxicity in the first 3 months of therapy.

MATERIALS AND METHODS
Ninety-three successive patients started on ART in our institutional ART centre were enrolled for this study. Base line parameters including clinical status, CD4 count and baseline investigation were done as per NACO guidelines. (1,4). They were followed for three months for clinical and lab evidence of toxicity. Laboratory monitoring was done as per NACO recommendations. The impact of toxicity on treatment interruptions were documented and analysed.

RESULTS
Following common early toxicity was observed in this study: anorexia and vomiting occurred in 44% (N = 24 + 17 pts) fatigue and anaemia in 26% (24 pts) pruritus and rash in 10% (9 pts).

6% patient had psychiatric manifestation and 7% (6 pts) had ALT elevation however hepatotoxicity was not found to be a major problem despite many patients being on ART and ATT simultaneously.

None of the patients with gastro-intestinal symptoms, psychiatric manifestation and ALT elevation needed change in ART due to toxicities. 5 of 9 (56%) patients who had skin reactions and 10 of 24 (42%) patients who had developed anaemia had to change their initial ART regimen. Stavudine for zidovudine in patients associated with anaemia and Nevirapine to Efavirenz in patients with skin reactions.

Minimal number of patients stopped their treatment for 1-2 weeks for rash, vomiting etc., underscoring the importance of this minor symptoms in patient compliance.

Age, gender, baseline CD4 count and concurrent ATT were not predictors of toxicity in our study, zidovudine was found to be significantly associated with occurrence of anaemia and Nevirapine with skin toxicity.

CONCLUSION
In this study of 93 HIV positive patients newly started on ART, the early toxicities observed were anorexia and vomiting, fatigue and anaemia, pruritus and skin rash, psychiatric manifestations and ALT elevations.

KEYWORDS
ART (Anti-Retroviral Therapy), ATT (Anti-Tuberculous Treatment), ALT (Alanine Transferase), ADR (Adverse Drug Reactions), ZLN (Zidovudine, Lamivudine and Nevirapine), SLN (Stavudine, Lamivudine and Nevirapine), SLE (Stavudine, Lamivudine and Efavirenz), TLE (Tenofovir, Lamivudine and Efavirenz).

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BACKGROUND
HIV infection has become a global pandemic.1-2 More than half of the children living with HIV/AIDS are females. A vast number of children have been orphaned by premature death of both parents due to AIDS placing enormous responsibility on society. Significant numbers of children are living with HIV/AIDS. India had largest burden of HIV/AIDS patients next to sub-Saharan Africa.

With advent of highly active anti-retroviral drugs, its prices getting less expensive and also being provided by ART centres in India an increasing number of HIV infected patients are receiving ART. However, the toxicity of ART drugs becomes an increasingly important issue in their management.

Adverse effects have been reported with virtually all anti-retroviral drugs. Sometimes they are life threatening leading to switching off or discontinuation of therapy and for medication non-adherence limiting its clinical efficacy.3,4
Despite the current anti-retroviral drugs being potent, they fail because of patient non-adherence. To optimize adherence and efficacy, clinician must focus on preventing adverse effects and also distinguish those that are self-limiting from those that are potentially serious. Treating physician must remain aware of new and developing syndromes associated with anti-retroviral use.

Objectives of the Study
To study the Adverse effects of antiretroviral drugs in the initial three months of therapy with regards to its severity, possible predictors of toxicity and the adherence to therapy.

MATERIALS AND METHODS
This was a prospective study undertaken between April 2015 and March 2016 on 93 consecutive patients attending the ART centre of Patna Medical College, Patna, who were seropositive for HIV and newly started on ART. Seropositivity was determined by established NACO guidelines. The patients were closely observed for 3 months for toxicity on OPD basis. Follow up were done at 2-4, 4-8 and 12-14 weeks. A detailed clinical evaluation with emphasis on toxicity profile of ART drugs was done on each visit.

RESULTS
The study population comprised of 47 males (50.5%) and 46 females (49.5%) with mean age of 36.81±10.33 years. Maximum numbers of patients were in the age group 30-40 years (49.5%) and minimum in group above 50 years (12.9%). Most of the patients 63(67%) were married and living with their partners, 22(23.7%) were widowed, 5(5.4%) divorced/separated and only 3(3.2%) were unmarried.

Most patients were educated up to 8th class 33(35.48%), illiterates comprised 30 (32.25%), graduates were least affected 7 (07.52%), house wives and drivers were most affected 41% and 12% respectively. All the patients had CD4 count <300 cells/cu mm at the initiation of ART. Nearly 71% patient had severe immune deficiency (CD4 <200 cells/cu mm). 19% patient had CD4 count <50 cells/cu mm and only 11% had CD4 count more than 250 cells/cu mm.

The regimens used were the standard NACO regimens.

Z- Zidovudine, L- Lamivudine, N- Nevirapine, S- Stavudine, E- Efavirenz, T-Tenofovir

Symptoms Signs and Investigation before ART initiation
Fatigue was present in 15%. Most of the patients were anaemic (61.3%) the baseline mean Hb was 11.41% (± 2.28 gm/dl) with range of 6.2-17.4 gm/dl.

A small number of patients (6.4%) had ALT elevation. The initial ART regimen used were standards NACO regimen.

<table>
<thead>
<tr>
<th>Symptoms and Signs</th>
<th>No. of Pt. with Adv Rk at 1-4 wks.</th>
<th>No. of Pt. with adv Rk at 5-8 wks.</th>
<th>No. of Pt. with adv Rk at 9-12 wks.</th>
<th>No. of Pt. with adv Rk at 13-14 wks.</th>
<th>Total No. Pt. with reaction</th>
<th>Change of ART Due to Side Effects</th>
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<tr>
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<tr>
<td>Pruritus</td>
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<td>Fever</td>
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<td>Fatigue</td>
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DISCUSSION
HIV infection has become pandemic and its incidence and prevalence is fast increasing. With the government starting ART centre throughout the country ART facility is getting increasingly available to nearly all HIV positive patients. One of the major determinants of success of ART regimen is compliance and major hurdle to compliance is drug toxicity. This study was planned to look into early toxicity that is first three months of therapy the most vulnerable period of patient drop out.

Adverse Events
During the study period of 3 months ART related toxicity developed in 48 patients (51%). Of these 17 (18%) were categorised as severe (grade 3-4). Two or more toxicities developed in 18(19%) patients. Sharma et al-2008, Harminder Singh et al 2009, Malangu et al 20083,4,9 found adverse effects to the tune of 71.1%, 86% and 94% respectively in their studies. Our low percentage could have been because short period of study.

The major adverse reactions in our study were Anorexia and vomiting (26%), Fatigue and anaemia (26%) followed by Pruritus and rash in (10%), Psychiatric manifestations (6%) and ALT elevations in (7%) respectively,

Our findings are quite different from that reported by Sharma et al where the chief ADR was cutaneous manifestation, of Harminder Singh et al with peripheral neuropathy and of Malangu et al reporting sexual disorders. Peripheral neuropathy and sexual disorders are probably late manifestations that is why it was absent in our study.

Anorexia/Nausea/Vomiting
17(18.3%) patients suffered anorexia and 24(25.8%) nausea and vomiting with peak incidence around 5-8 days of ART. 2 patients stopped their ART for a week on their own.

Nausea and vomiting usually resolved with time and were managed with antiemetics and proton pump inhibitors without a change in ART regimen.

Nausea/ vomiting can be troublesome for the patients and can lead to poor compliance. It is important to counsel the patient and treat them symptomatically to avoid non-compliance and discontinuation of treatment.

Diarrhoea
Only 2 patients developed diarrhoea in our study and that too in the 4th week of treatment and that resolved with OPD treatment without any change in ART regimen. Diarrhoea is most commonly caused by didanosine, tenofovir and protease inhibitors. Only 12.90% of our patients were on tenofovir which may be a reason for less number of patients with diarrhoea in our study group.

Drug Hypersensitivity (Rash and Pruritus)
Rash developed in 9 patients out of which only 7 had pruritus. All the patients having rash were on Nevirapine based ART i.e. 13.4% of Nevirapine group. Two of them had fever also.

Almost all patient developed rashes during first 4 weeks of therapy, only one had between 9-12 weeks. 5 patients had to change to Efavirenz due to severe reaction (single drug substitution). One death occurred due to toxic epidermal necrolysis (TEN)

Skin reactions seem to be the most serious of early toxicities and our study highlights the importance of this side effect in patients on ART. It can become serious to life threatening and needs close monitoring as many will need interruption of ART because of the rash compromising the treatment and change of regimens. One patient was switched onto Efavirenz based regimen which was tolerated well.

Psychiatric Disorder
6 (6%) patients had insomnia and night mares. Four at 1-4 weeks and 2 at 5-8 weeks of therapy. They were all on Efavirenz based regimen. None had adverse outcome or required change in ART.

Anaemia
24 (26%) patient had significant drop in their Hb level after initiation of ART (18 with detectable pallor). However, drug interruption was not warranted in them. Fatigue and anaemia persisted throughout the study period with maximum incidence observed at 8-10 weeks’ time of ART. 23 of 24 patients who developed anaemia were on zidovudine-based regimen and 10 of them were changed to Stavudine based regimen because of anaemia progressing.

The remaining patients continued on zidovudine-based regimen as their anaemia was mild (grade 1 toxicity WHO grading).

In our study incidence of anaemia was not associated with baseline characteristics i.e. gender, age, baseline CD4 count and concurrent tuberculosis treatment. However, Kenneth A. Lichtenstein et al found increased incidence with female gender, baseline CD4 count <200 cells/cumm, baseline Hb-1 median value and zidovudine was the only factor for development of anaemia (p=0.035).

ALT Elevation on ART
7 (7.5%) of our patients had elevation of ALT in follow up (minimal grade 1 toxicity). In a study done in Thailand 6.7% patient had grade 3-4 laboratory toxicity. Increased incidence of co infection with hepatitis B or hepatitis C in their patients could be responsible for the increased severity of toxicity.

<table>
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<tr>
<th>Pallor</th>
<th>5</th>
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<tr>
<td>Nightmares &amp; insomnia</td>
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</table>

Table 1. Summary of Toxicities Observed
The hepatotoxicity was not affected by gender, age, baseline CD4 level and concurrent tuberculosis treatment similar to other studies done in Uganda and South Africa.\textsuperscript{10}

**Toxicity: Grading or Severity**

Our study had grade 4 toxicity in 4 (4.3%) patients: one TEN; 3 anaemia; grade 3 in 13 (13.9%) patients - 4 skin reactions and 9 anaemia; grade 2 in 10 (10.8%) patients as 1 skin reaction, 3 anaemia and 6 vomiting; grade 1 in 43 (46.2%) patients - 4 skin reactions, 18 GI reactions, 10 anaemia, 6 with nightmares, and 7 ALT elevations. Our findings are consistent with the observations of Harminder Singh et al.\textsuperscript{3}

Minors reactions are extremely common (50%) and can lead to non-compliance of drugs. It is imperative to counsel the patient about common minor toxicities and more importantly about the warning signs of more serious toxicity that is skin reactions, jaundice etc. so that severe morbidity and mortality could be avoided

**Toxicity and Medication Change**

Of the 93-patient initiated on ART the majority 71 (75.3%) did not require change in ART. Only 22 (24.7%) required change. Reason for changing ART was anaemia -10 patients, skin reactions—5 patients, starting of ATT in 3 patients and completion of ATT in 4 patients. Drugs toxicity accounted to ART regimen change in only 15% patients.

Anaemia was the most common cause for change of ART (Zidovudine to Stavudine) in our study. However, the treatment was not interrupted. Skin reactions were the major cause of treatment interruption. The drugs were reintroduced only after the reactions had subsided.

In a study by Sharma et al\textsuperscript{8} rash, peripheral neuropathy, anaemia, hepatotoxicity were reported as most common toxicity interfering with adherence. In our study hepatotoxicity was not a problem for interruption. In contrast in a study by Royal free hospital, Efavirenz induced neuropsychiatric manifestations were reported to be the most common cause of initial ART change.

**Toxicity and Adherence**

A total of 7 (7.5%) patients had treatment interruption due to toxicity. Sharma et al found 17 (19%) out of 90 cases non-adherent to medications and ADR was the most common reason for irregular treatment in 5 (5.5%) cases. Drugs toxicities are important cause for treatment interruptions and non-compliance during early period of ART treatment and needs adequate redressal.\textsuperscript{3,4,9}

**Predictors of Toxicity**

No association was found between baseline characteristics and toxicity including age, gender, base line CD 4 count and concurrent TB treatment. Even hepato-toxicity was not marked in many patients taking concurrent ATT.

Nevirapine based regimens were significantly associated with skin reactions (p=0.018) and Zidovudine based regimens with development of anaemia (p=0.035) which is well documented in previous studies.\textsuperscript{11}

**CONCLUSION**

In this study of 93 HIV positive patients newly started on ART the early toxicities observed were anorexia and vomiting, fatigue and anaemia, pruritus and skin rash, psychiatric manifestations and ALT elevations.

Skin reaction seems to be the most serious of early toxicities and is most common cause of treatment interruption in ART. A rash in a patient on ART requires close follow up as it could be harbinger of a serious life-threatening reaction. In our study, the only mortality was due to TEN.

Gastro-intestinal symptoms i.e. diarrhoea and vomiting though not very serious could be troublesome for the patients and was the only other cause of treatment interruption in our study. This underscores the importance of this minor side effect in the continuation of treatment.

Anaemia secondary to Zidovudine is common but was managed with a single drug substitution and without treatment interruption.

Hepatotoxicity was not found to be very alarming in our study despite many patients on concurrent ATT administration. Treatment interruptions due to toxicities occurred in 7.5% of our patients in the first three months of treatment, making this an important issue to be considered while the patient is on ART.

**REFERENCES**


