SPECTRUM OF ADVERSE EFFECTS OF HAART THERAPY AMONG HIV INFECTED INDIVIDUALS- A PROSPECTIVE STUDY

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ABSTRACT

BACKGROUND

India is the world's second largest country with HIV. The prevalence of HIV among Indian adults is 0.26%. In 2015, India had 2.1 million people living with HIV. HAART has reduced HIV mortality significantly. It is clear now that prolonged treatment that maintains suppression of plasma viraemia is unlikely to eradicate HIV. Therefore, therapy must be lifelong. Unfortunately, up to 25% of individuals discontinue HAART due to treatment failure, toxic effects or noncompliance.

The aim of the study is to study prospectively various HAART drugs induced adverse reactions among HIV patients within 6 months of therapy. To evaluate the correlation between the adverse drug reactions with various demographic factors, clinical symptoms at the time of initiation of treatment, CD4 count at the baseline and various HAART regime.

MATERIALS AND METHODS

200 HIV patients who fulfilled the NACO Guidelines for HAART therapy were started on treatment. All the investigations were done as per NACO Guidelines - Hb%, RBC indices, TC, DC, platelet count, peripheral smear morphology, blood sugar, lipid profile and CD4 count. Categorical measurements are presented in number (%). Chi-square test has been used to find out the significance of study parameters on categorical scale between 2 or more groups.

RESULTS

Out of 200 patients who were prospectively studied from January 2015 to October 2016, 60% had various adverse drug reactions. The M:F was 1.2:1 with a mean age of 37.2 ± 8.5 (23-66 yrs.), 32.1 ± 10.1 (16-70 yrs.), respectively. None of the demographic factors showed any relation with ADR. Gastrointestinal manifestations are most common ADR (40.8%) followed by fatigue (25.9%). Nevirapine base regime significantly associated with dermatological manifestations ($p=0.008$). Peripheral neuropathy correlated significantly with the stavudine usage ($p=0.05$). None of our patients were noncompliant with treatment.

CONCLUSION

Adverse drug reactions are common during early part of HAART. Gastrointestinal manifestations are most common during this period. Most of the adverse drug reactions can easily recognised and early treatment will not affect the adherence pattern with HAART.

KEYWORDS

HIV, HAART Therapy, Adverse Effects.

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BACKGROUND

India is the world's second largest country with HIV. HIV virus was first recognised in India in 1986. One of every 6 HIV patients is in India. The prevalence of HIV among Indian adults is 0.26%. In 2015, India had 2.1 million people living with HIV. HAART has reduced HIV mortality significantly. It is clear now that prolonged treatment that maintains suppression of plasma viraemia is unlikely to eradicate HIV. Unfortunately, up to 25% of individuals discontinue HAART due to treatment failure, toxic effects or noncompliance. Moreover, adverse drug effects have been increasingly recognised recently as the incidence of

opportunistic infections have been significantly reduced. The risk of the specific adverse effects varies from drug to drug, regime to regime and patient to patient. Due to the ongoing development of newer antiretroviral drugs, it become much more important to understand and recognise the various adverse effects for better management.

Despite HAART therapy has been introduced in India since many years, there are only very few studies have been comprehensively looked into various adverse effects and majority of the studies have been limited to certain aspects of whole spectrum of adverse effects. In this study, various adverse effects related to HAART drugs among Indian patients have been studied prospectively.

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Name	Dosage	Adverse Effect
Nucleoside Reverse Transcriptase Inhibitors		
Zidovudine	300 mg b.i.d. tablet; 10 mg/mL oral, IV solution	Nausea, vomiting, headache, asthenia, anaemia, neutropaenia
Stavudine	40 mg b.i.d. tablet; 1 mg/mL oral solution	Peripheral neuropathy, pancreatitis, lactic

		acidosis, lipoatrophy, hyperlipidaemia
Lamivudine	150 mg q.i.d. tablet; 10 mg/mL oral solution	Minimal toxicity
Tenofovir	300 mg q.i.d. tablet	Nausea, vomiting, diarrhoea, headache, asthenia, renal insufficiency
Non-Nucleoside Reverse Transcriptase Inhibitors		
Nevirapine	200 mg tablet b.i.d.; 10 mg/mL oral solution	Rash, hepatitis
Efavirenz	600 mg q.i.d. tablet	Rash, CNS (vivid dreams, somnolence, confusion, visual hallucinations)
Protease Inhibitors		
Indinavir	800 mg b.i.d. tablet	Nephrolithiasis, nausea, indirect hyperbilirubinaemia, hyperlipidaemia, hyperglycaemia
Ritonavir	100 mg tablet soft gelatin capsule	Nausea, vomiting, diarrhoea, asthenia, oral parasthesia, hyperlipidaemia, hyperglycaemia
Integrase Inhibitors		
Raltegravir	400 mg b.i.d. tablet	Nausea, diarrhoea, headache, myopathy/rhabdomyolysis
Chemokine Receptor (CCR5) Antagonist		
Maraviroc	150 mg b.i.d. tablet	Constipation, dizziness, infection, rash
Fusion Inhibitor		
Enfuvirtide	90 mg SC Inj. b.i.d.	Inj. site reactions (pain, erythema, induration, nodule)

With the advent of HAART, HIV-1 infection is now manageable as a chronic disease in the patients who have access to medication and achieve durable virologic suppression.

6 classes of antiretroviral agents exist. Each class targets a different step in a viral lifecycle as the virus infects CD4 T lymphocytes and other target cells. The use of these agents in a practice largely dictated by their ease or complexity of use and side effect profile and clinical preference.

Commonly used Drugs in HAART Therapy-

Currently, the National Programme provides the following combination for first line regimes.

1. First choice- Zidovudine (AZT) + lamivudine (3TC) + nevirapine (NVP) (for the patients with HB >8 gm%).
2. Second Choice- Tenofovir (TDF) + lamivudine (3TC) + efavirenz (EFV).
3. Third Choice- Stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP)/efavirenz (EFV).

Objectives

1. To study prospectively various HAART drugs-induced adverse reactions among HIV patients within 6 months of therapy.
2. To evaluate the correlation between adverse drug reactions with various demographic factors, clinical

symptoms at the time of initiation of treatment, CD4 count at baseline various HAART regime.

MATERIALS AND METHODS

The study was conducted during the period from January 2015 to October 2016 at ART Center, Government General Hospital, Anantapur, Andhra Pradesh.

During the study period, 200 HIV patients who fulfilled the NACO Guidelines for HAART therapy were started on treatment and recruited for the study with following inclusion criteria. All HIV positive patients irrespective of associated opportunistic infections, those patients who started HAART therapy within 6 months of initiation of study were also recruited. None of the patients were excluded unless they are not willing to participate in the study.

Classification of HIV Associated Clinical Diseases	WHO Clinical Stage	CD4 Test not Available	CD4 Test Available
Asymptomatic	1	Do not treat	Start ART if CD4 <350/cu. mm.
Mild symptoms	2	Do not treat	Start ART if CD4 <350/cu. mm.
Advanced symptoms	3	Treat	Start ART irrespective of CD4 count
Severe symptoms	4	Treat	Start ART irrespective of CD4 count

Table 1. NACO/WHO 2015 Guidelines for Initiation of the HAART

All the patients who were attending the ART Centre OPD were interviewed by single investigator and details were entered in the predesigned proforma for subsequent analysis of the data.

Details about various demographic information, clinical features with regards to HIV with or without associated OI. All the patients underwent detailed clinical examination as per proforma. All newly-recruited patients came for the followup at 1, 3 and 6 months. At every followup visit underwent detailed clinical evaluation with special emphasis on any new symptoms that has been observed after initiation of HAART therapy or any worsening of pre-existing symptoms. Specialist's opinion was taken regarding various clinical features such as peripheral neuropathy, nightmares, dermatological manifestations, etc. All the investigations were done as per NACO Guidelines done at our central laboratory. We grouped the HAART regime basically into 2 types based on the use of nevirapine based regime- AZT+3TC+NVP, efavirenz-based regime- TDF+3TC+EFV.

Investigations include complete haemogram, which include Hb%, RBC indices, TC, DC, platelet count, peripheral smear morphology, blood sugar and lipid profile, if patient on protease inhibitors, urea and creatinine, if renal dysfunction is considered, liver function tests was done at baseline 1, 3 and 6 months. Serum lactate, anion gap estimation and ABG was done those who presented with clinical signs and symptoms of lactic acidosis. CD4 counts, VDRL, HbsAg and HCV was done as per NACO Guidelines. The study was approved by hospital ethics committee. Descriptive statistical analysis was carried out in present study. Results on continuous measurement are presented on mean +/- SD.

Results on categorical measurements are presented in number (%). Chi-square test has been used to find out the significance of study parameters on categorical scale between 2 and more groups.

RESULTS

We evaluated the correlation between lower CD4 counts with various demographic factors by dividing the CD4 counts into <100 cells/cu. mm.- 101-200 cells- >200 cells. In our study, the younger age population (30-50 yrs.) was severely immunocompromised with CD4 count <200 cells/cu. mm. Out of 73 individuals in the age category is 21-30 years, more than half of them (38 out of 73) had CD4 count <200 cells/cu. mm. and 15 out of these 38 had <100 cells/cu. mm. In the age category of 31-40 years, 54 of 72 had CD4 count <200/cu. mm. Among them, 32 had <100/cu. mm. Between 41-50 yrs. of age, 26 of 38 had count CD4 <200/cu. mm. Among them, 12 had <100/cu. mm. Interestingly, all individuals (5) between 61-70 yrs. had CD4 count <200 cu. mm and 3 of these 5 are severely immune compromised with CD4 count <100/cu. mm. Thus, in our study, younger age individuals had more severe immunodeficiency by the virtue of lower CD4 counts ($p=0.011$).

We found that in our population, male gender had significantly lower CD4 count than female ($p=0.05$). Out of 109 male patients studied, 78 had CD4 <200 cells/cu. mm. Nearly, half of them had <100 cells/cu. mm. Among the female patients, 54% had <200 cells/cu. mm. Severe immunodeficiency with count <100 cells/cu. mm was observed in 23 of 52 patients.

The other demographic factors such as educational status ($p=0.283$), occupation ($p=0.802$), income status ($p=0.059$) didn't show any statically significant correlation with CD4 count. We analysed the correlation between presenting clinical symptoms with baseline CD4 count. Most of the common symptoms such as fever ($p=0.017$), weight loss (0.058), loss of appetite (0.017), cough (0.074), diarrhoea (0.583), etc., correlated significantly with lower CD4 counts. We didn't notice any statically significant association between lower BMI and low CD4 counts.

We had 111 patients with various forms of OI (PTB, Herpes zoster, etc.). 76 patients had CD4 <200/cu. mm. and 35 had CD4 >200/cu. mm. Severe immunodeficiency with CD4 <100 was seen in 45 of 76. There was significant correlation between lower CD4 counts and higher prevalence OI.

In our study, the overall prevalence of early ADR within 6 months of initiation of HAART was 60% (120 of 200). Overall, there are 255 ADR events in these 120 patients. The most common ADR was related to involvement of GI system. Nausea and vomiting was prevailed in 57 events (22.4%). The symptoms of acute gastritis such as dyspepsia, retrosternal burning sensation, epigastric discomfort, pain in abdomen was seen in 44 (17.3%). Only 3 had acute drug-induced hepatitis.

Overall, 40.8% ADR was related to GI system. Out of 255 events, 66 were related to fatigue (25.9%). Most of these events occur during initial period of HAART. Anaemia was observed in 44 events (17.3%). Majority of them are on AZT. Dermatological manifestations such as various types of skin rashes and hyperpigmentation of nails was observed in 18 events (11.1%). Most of them were NVP-based regime. 13

events are characterised by dull aching holocranial headache (5.1%). We had an immune reconstitution inflammatory syndrome in 4 patients (1.6%). All 4 patients with immune reconstitution inflammatory syndrome has coexisting TB. Peripheral neuropathy was observed in 2 patients (0.8%). Both of them were on STV-based regimen. One of the patients on EFV complain of nightmares, disturbed sleep and excessive daytime sleepiness. We had 2 patients of signs and symptoms of lactic acidosis presented with complaints of nausea, vomiting and abdominal discomfort. All patients had increased anion gap, elevated fasting serum lactate levels. One of these on STV, another on AZT. However, the patients who had loss of weight as an initial presenting symptom had a trend towards statistically significant correlation with high prevalence of ADR ($p=0.088$). Leucopenia was prevalent in 56.5% of our patients. Majority of our patients showed the lower HDL levels.

Maculopapular Drug Rash Due to Efavirenz

Zidovudine-Induced Nail Pigmentation

Lipodystrophy

Immune Reconstitution Inflammatory Syndrome Cervical Lymphadenopathy

Immune Reconstitution Inflammatory Syndrome Cervical Lymphadenopathy

DISCUSSION

We found most common ADR was related to involvement of GI system manifestations such as acute gastritis, nausea, vomiting as well as drug-induced hepatitis¹ (40.8%). In contrast to our observation, Harminder Singh et al (2009) reported peripheral neuropathy as most common ADR (31.64%). Kumara Swamy et al (2002) and Ajay Sharma et al² (2008) reported cutaneous manifestations as most common ADR (15.2% and 44.4%, respectively). This difference in various studies could be due to difference in the drugs used during the initiation of HAART and different periods of follow up.

Most of the HAART drugs from NRTI and PI are associated with GI and hepatic toxicities, but cutaneous ADR are most common with NNRTI's.

None of the studies have looked at the prevalence of the fatigue after the initiation of HAART therapy, which could be one of the commonest yet unrecognised ADR, which may force the patient to default therapy. In our study, second most common ADR was fatigue as evaluated by questionnaire (25.9%). The overall prevalence of anaemia in the present study was 17.3% and 15% of them are severe anaemia. Harminder Singh,³ Kumaraswamy and Ajay Sharma reported anaemia as ADR in their 13.3%, 5.4% and 20% of their patients respectively. All of our patients were treated with iron and folic acid supplementation. This observation was not made in earlier studies.

Pattern of Adverse Reactions	Number of Events (n=255)	Percentage
Fatigue	66	29.5
Nausea/vomiting	57	22.4
Gastritis	44	17.3
Anaemia	44	17.3
Rashes	18	7.1
Headache	13	5.1
Immune reconstitution inflammatory syndrome	4	1.6
Hepatitis	3	1.2
Lactic acidosis	2	0.8
Peripheral neuropathy	2	0.8
Nightmare	1	0.4
ADR with drugs for OI	1	0.4

Table 2. Pattern of Adverse Reactions of HAART Therapy

The prevalence of peripheral neuropathy in our cohort (0.8%) was lower compared to other studies. Harminder

Singh reported it as most common ADR in their cohort who were followed up for 2 years. Similarly, Ajay Sharma reported 22.2% and Kumaraswamy 9%. All these authors including present study found that stavudine-based regimes commonly associated with higher prevalence of peripheral neuropathy. The reasons for lower prevalence in our study could be due to shorter follow up and less number of patients on stavudine regime.

Lactic acidosis is one of the severe forms of ADR seen with AZT and stavudine. In our current study, there were 2 patients who have elevated lactate levels with increased anion gap. Ajay Sharma reported it in 1 in 90 patients. The prevalence of lactic acidosis varies from 10-20% (Tesiorowsky AM). These patients treated with change in the regime after discontinuation of HAART for short period.

In our study, immune reconstitution inflammatory syndrome was observed in 4 patients (1.6%) and all of them were presented with tuberculosis. Immune reconstitution inflammatory syndrome was reported in 22.2% of patients by Ajay Sharma. 11 patients presented with Herpes zoster, 5 with Herpes simplex and 4 patients with new onset of TB in his study.

Lipodystrophy commonly associated with treatment of PI and stavudine. Harminder Singh and Ajay Sharma reported it in 20% and 14.5% of their patients, respectively. In contrast, we did not notice lipodystrophy in any of our patients. This could be possibly due to non-utilisation of PI and less number of patients on STV.

Nightmares and vivid dreams were observed in one of our patients on EFV-based regime. Similarly, Ajay Sharma observed the same in 2 of their patients on EFV.

In this study, we attempted to correlate between various ADR and baseline CD4 count instead of medium CD4 count at the time of event. Except anaemia, which showed a positive trend towards statistically significant correlation with lower CD4 count at the time of initiation, none of the other individual events correlated significantly with CD4 counts. Harminder Singh concluded that lower CD4 count correlated significantly with overall prevalence of ADR with HAART.

We also attempted the correlation between various demographic factors with the prevalence of ADR. None of the demographic factors influenced the prevalence of ADR in our study.

Similarly, when we analysed the correlation between the BMI and stage of the disease at the time of inclusion, there was no statically significant relation. However, those patients who had loss of weight at the time of initiation of therapy showed a positive trend towards higher chances of ADR.

There were few attempts to correlate between regimen selected for initiation of HAART and prevalence of ADR. The skin rashes were significantly correlated with NVP-based regime and peripheral neuropathy had significant correlation with stavudine-based regimen.

In this study, lower CD4 counts significantly correlated with younger population and male gender suggesting that these subjects were probably more sexually active acquiring more virulent form of virus, which leads to more severe immunosuppression. The clinical symptoms at presentation correlated significantly with lower CD4 counts suggesting lower immune status. Similarly, the more severe the disease stage at presentation, the lower CD4 counts. Opportunistic infections occurred more commonly with lower CD4 counts.

All these findings only reinforced the already established phenomenon with respect to lower CD4 counts and their consequences.

CONCLUSION

ADR common even with short duration of HAART therapy. Gastrointestinal manifestations are more common during early part of therapy. Fatigability due to HAART is also one of the common ADR, which needs to be systemically addressed to increase the compliance with the treatment. Some of the authors observed female gender are more susceptible to ADR. We did not notice this gender difference. ADR are not influenced by age, educational status, income, lower BMI, advanced stage of disease and lower CD4 count at the time of initiation of therapy. None of our patients were noncompliance with HAART despite of 2/3 of them suffered from ADR. This suggests that early reactions can be effectively managed by early recognition and treatment, which will increase success rate of HAART and quality of life. To optimise adherence and efficacy, clinicians must focus on preventing this ADR whenever possible and distinguishing

those that are self-limited from those that are potentially serious such as lactic acidosis. More research is needed to develop low-cost investigations and algorithm for prediction of ADR to existing regimes along with generations of more efficient and less toxic drugs.

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