Research Article

Adverse drug events due to Antiretroviral Therapy in a Northern Indian Tertiary Care Institution

Shamiya Sadiq[1], Sapna Gupta[1], Vijay Khajuria[1], Vishal R Tondon[1], Annil Mahajan[2], Mrityunjay Gupta[3]

[1]Department of Pharmacology, Govt. Medical College, Jammu, J & K, India.
[2]Department of Medicine, Govt. Medical College, Jammu, J & K, India.
[3]Department of Physiology, Govt. Medical College, Jammu, J & K, India.

Correspondence to: Shamiya Sadiq, E-mail: drshamiya31621@gmail.com

Received January 31, 2016. Accepted February 13, 2016

Abstract

Background: The introduction of highly active antiretroviral therapy (HAART) has led to significant reduction in acquired immune deficiency syndrome (AIDS) related to morbidity and mortality. However, adverse drug reactions (ADRs) to antiretroviral treatment (ART) are major obstacles. **Aims and Objective:** To examine the adverse effects of antiretroviral therapy in a tertiary care hospital. **Materials and Methods:** Ninety patients receiving antiretroviral therapy were studied prospectively over a period of 6 months and were evaluated for ADRs. **Result:** Of the 90 patients, 80 (89%) developed ADRs. A total of 111 ADR events were seen in 80 patients. The number of adverse drug events was seen higher in females (64%) than males (36%). The maximum frequency of ADRs was seen with Zidovudine + Lamivudine + Nevirapine (70.27%) combination followed by Stavudine + Lamivudine + Nevirapine (21.62%) and Stavudine + Lamivudine + Efavirenz (8.10%). Anemia and gastritis (12% each) were most common ADRs followed by vomiting (11.7%) and rash (10.8%). Most of the adverse drug events (ADE) were of type A (83.78%). The severity of most of the ADR events was mild (70.27%), followed by moderate (27.02%) and severe (1.78%). **Conclusion:** ADRs are common with HAART. Maximum number of ADRs occurred in females and Zidovudine + Lamivudine + Nevirapine (70.27%) combination was the main culprit. To minimize the potential risks of ADR due to ART, the clinicians need to detect them earlier and prevent them whenever possible and choose drugs with safer adverse drug profile.

KEY WORDS: ADRs; Adverse drug events; Anti-retroviral therapy; HAART; HIV

Introduction

Human immunodeficiency virus (HIV) infection is a global pandemic with 35 million people living worldwide.[1] India too has a concentrated HIV epidemic with substantial geographical variation. The epidemic peaked in the 1990s and in 2009, there were an estimated 2.4 million (1.8–2.9 million) persons living with HIV.[1,2]

Access this article online	
Website: http://www.njppp.com	Quick Response Code:
DOI: 10.5455/njppp.2016.6.31012016114	

Anti-retroviral therapy (ART) has improved the prognosis for people living with HIV-infection/acquired immunodeficiency syndrome (AIDS) (PLHA). There has been reduction in mortality with increased use of potent antiretroviral drugs generally administered in a combination of three or four agents.[3] Most of the drugs available and approved for use in highly active antiretroviral therapy (HAART) have some or the other adverse effects.

Serious side effects are more varied with nucleoside analogs (zidovudine, didanosine, stavudine, lamivudine, tenofovir, etc.) including mitochondrial damage that can lead to lactic acidosis as well as peripheral neuropathy and pancreatitis. HAART therapy has also been associated with

lipodystrophy syndrome of hyperlipidemia and fat redistribution.[4] Among the other side effects are fatigue, malaise, nausea, anemia, and hepatotoxicity. Non-nucleoside inhibitors, nevirapine and efavirenz are used in combination with nucleoside analogs for the treatment of HIV and are associated with the development of a maculopapular rash, dizziness, feeling of lightheadedness. [3,4]

Since there is paucity of data regarding ADR in relation to drugs in the management of HIV, therefore, this study was undertaken to study the ADR pattern and establish the cause and effect relationship of each ADR of anti-retroviral drugs in patients with HIV.

Material and Methods

This prospective observational study was conducted in Department of Pharmacology and Therapeutics in collaboration with the Anti-retroviral Therapy Centre, Department of Medicine, Government Medical College, Jammu over a period of 6 months after approval from institutional ethical committee. The eligible subjects were recruited from the ART center and OPD. All HIV positive patients attending ART OPD or admitted in medicine wards already on ART and those who were newly started on ART and patients who develop at least one ADR during the period were included in the study. All common prevalent communicable and noncommunicable diseases present in HIV patients, medication errors, and poisoning were excluded from the study. In cases where same patient experienced an identical reaction more than once, the patient was documented as having experienced a single reaction.

Initially a total of 90 patients were included in the study. All patients stratified as per the initiation of ARV therapy (WHO clinical staging 3/4th or clinical stage 1/2 with CD^{4+} T-cell count less than 300 cells/μL). A detailed history of each patient and baseline laboratory investigations were done. A predesigned performa was used to record ADRs which included onset, severity, treatment, and outcome.

The cause and effect relationship of each ADR because of anti-retroviral drugs was assessed using Naranjo's Probability scale.[5] The Naranjo's algorithm, a questionnaire designed consists of objective questions with three types of responses—yes, no, or do not know. Scores are given accordingly and the drug reaction can be classified as highly probable, probable, possible, or doubtful.

The severity of the ADR was assessed using the Modified Hartwig and Siegel scale[6] which classifies severity of ADR as "mild" (bothersome but requires no change in therapy), "moderate" (requires change in therapy, additional treatment, and hospitalization), and "severe" (disabling or life-threatening). The types of ADR were be classified as A, B, C, and D as per Rawlins and Thompson.[7]

Detailed evaluation of the case sheets was done. The patient information, drug-related suspected ADR, medicine-related information was analyzed. The 'Suspected Adverse Drug Event Reporting Form' was used. The clinical profile and the important information related to ADR in the form of patient's brief history including any past history of ART intake, clinical presentation, relevant laboratory investigations, diagnosis, drug therapy, and the treatment outcome was entered in these forms.

Art Regimens

1. Zidovudine (300 mg) + Lamivudine (150 mg) + Nevaripine (200 mg)
2. Stavudine (30 mg) + Lamivudine (150 mg) + Nevaripine (200 mg)
3. Stavudine + Lamivudine + Efavirenz (600 mg)

The recommended dosage used were as per NACO guidelines. Patients having hemoglobin >10 g% were initially put on Z + L + N combination, those having <10 g% were put on S + L + N combination.

Result

As some patients had more than one ADR event during the study period, the total number of ADE's was greater than the total number of patients experiencing a reaction. In this study, a total of 80 patients (89%) out of 90 developed ADRs, out of these 46 patients (57%) were females and 34 patients were males (43%). A total of 111 ADR events were seen in 80 patients more in females (63.96%) than males (36.03%). Number of ADR events were greater than the total number of patients since some patients had more than one ADR during the study period (Table 1).

Of the 80 patients, 52 (65%) received ZLN combination (zidovudine 300 mg + lamivudine 150 mg + nevirapine 200 mg) followed by SLN combination (stavudine 30 mg + lamivudine 150 mg + nevirapine 200 mg) in 17 patients (21.25%) and SLE combination (stavudine 30 mg + lamivudine 150 mg + efavirenz 600 mg) in 11 patients (13.75%). Of the 111 adverse drug events (ADE's) observed during the study, the maximum number of ADE's were seen with zidovudine + lamivudine + nevirapine (70.27%) combination followed by stavudine + lamivudine + nevirapine (21.62%) and stavudine + lamivudine + efavirenz (8.10%) (Table 2).

Distribution of ADR events reveal that anemia and gastritis (12.6% each) were most common, followed by vomiting (11.7%), rash (10.8%), loss of appetite, and sedation (9% each), lipodystrophy (8%), esophageal candidiasis (6.3%), diarrhea, giddiness, and hepatic dysfunction (5.4% each), peripheral neuropathy (2.7%), and fever (0.9%) (Table 3).

Of the 111 adverse drug events, 93 (83.78%) were of type A followed by 18 (16.21%) with type B. While based on severity,

Table 1: Showing gender and total number of ADEs

Gender	Total patients (n)	Total number developed ADE (n)	ADE (%)
Female	46	71	63.96
Male	34	40	36.03
Total	80	111	100

Table 2: Distribution of patients according to art regimen

HAART regimens	Total patients (n = 80)	Total number developed ADE (n = 111)	ADE (%)
Z + L + N	52	78	70.27
S + L + N	17	24	21.62
S + L + E	11	9	8.10

Table 3: Distribution of type of ADR events (n = 111)

Types of ADR	n	%
Anemia	14	12.6
Gastritis	14	12.6
Vomiting	13	11.7
Rashes	12	10.8
Loss of appetite	10	9
Sedation	10	9
Lipodystrophy	9	8
Oesophageal candidiasis	7	6.3
Diarrhoea	6	5.4
Giddiness	6	5.4
Hepatic dysfunction	6	5.4
Peripheral neuropathy	3	2.7
Fever	1	0.9

78 (70%) events were mild followed by 31 (27.9%) moderate and 2 (1.8%) severe events (Table 4).

As per Naranjo scale when ADR events were evaluated for causality, it was observed that majority (93.69%) of the events were possible in nature with score of 1–4. While the remaining (6.30%) were probable in nature having a score between 5 and 8 (Table 5).

Discussion

Ninety patients of HIV/AIDS on fixed dose combinations of ART were evaluated for adverse reactions over a period of 6 months. Of them 80 patients (89%) developed total 111 ADR events as

Table 4: Distribution of ADR events as per type and severity (n = 111)

Type of ADR	n	Percentage
A	93	83.78
B	18	16.21
Total	111	100
Classification of severity		
Mild	78	70.27
Moderate	31	27.92
Severe	2	1.8
Total	111	100

Table 5: Causality of ADR events as per Naranjo's probability scale (n = 111)

Score	Naranjo's scale	n	%
9	Highly probable	0	0
5–8	Probable	7	6.30
1–4	Possible	104	93.69
0	Doubtful	0	0

in some patients more than 1 ADR was observed. In this study, ADRs were seen more in females (63.96%) which are comparable to observation made by other research workers.[8,9] However, in contrast to our results a study has recorded higher ADRs in male population (53.5%).[10] Similar to our observations, various research workers have also observed high incidence of ADRs ranging between 71% and 86%.[11–13]

The most common side effect observed in this study was anemia and gastritis with incidence of 12.6% each. Anemia has been reported as the most common side effect with ART.[13] In this study, zidovudine + lamivudine + nevirapine based combination was prescribed in majority of the patients and zidovudine being a myelosuppressive drug is known to cause anemia within 3 months of initiating therapy. This could be reason for high incidence of anemia in this study .These results are comparable with previously reported studies.[14,15]

Gastritis (12.6%), vomiting (11.7%), and diarrhea (5.4%) were gastrointestinal side effects observed in this study. Identical to our observation similar results have been reported in 10% patients on ART who experienced gastritis.[11] Gastrointestinal side effects comprised of diarrhea, vomiting, pain abdomen has been reported in past with most of anti-retroviral drugs and are common cause of short-term discontinuation.[13]

Incidence of rash of 10.8% was observed in this study. Numerous reports have documented rash with ART therapy mainly with nevirapine.[11,12,16–18] Drug hypersensitivity in form of rash occur with HAART therapy usually in first 6 weeks of therapy.[19] Nevirapine, delavirdine and efavirenz, abacavir, amprenavir cause rashes frequently due to hypersensitivity which usually resolve spontaneously.[16]

Hepatitis with raised liver enzymes also a hypersensitivity manifestation occurred in 5.4%. Similar to our result, number of reports have recorded incidence of hepatitis ranging between 1.5% to 5.5%.[11,17,18,20] Among ART, nevirapine has been documented as one of the common cause of hepatitis.[21]

Lipodystrophy was seen in 8% patients. Stavudine associated lipodystrophy is common and is a multifactorial due to endocrine and metabolic abnormalities.[15,19] In concurrence to our report, 2.3% incidence has been recorded in earlier study.[13]

Peripheral neuropathy was observed in 2.7% patients. Peripheral neuropathy is mainly seen with stavudine, didanosine, and zalcitabine.[22] These inhibit nerve growth factor and result in neuropathy 1.3–22.3% of prevalence has been documented.[11,13,17]

It was important to examine causality according to Naranjo's scale of the suspected drug reaction in order to determine

whether drug discontinuation is mandatory, as well as to put emphasis on patient education to avoid adverse events in the future. As per Naranjo's scale majority of patients in this study were possible (93.69%) which is comparable to observation by other research workers.[23,24]

Conclusion

From the results of this study, we conclude that ADR events are quite common in patients with ART. Most of the ADRs were seen with zidovudine-based combination. Frequency of AEs was slightly more in females compared to males. GIT adverse effects were more common. Majority of ADRs were type A and mild in severity. Therefore, the early detection and reporting is of immense importance for better patient care as otherwise it may compromise adherence to therapy. Patients also need to be educated about ADR events as it leads to early ADR detection. Monitoring of adverse effects will help in further formulating rational regulatory decisions so that drugs with worse adverse profile are avoided.

References

1. UNAIDS Report on Global AIDS Epidemic 2013. Available at: http://www.unaids.org/globalreport/Global_report_2013_en_pdf [accessed Dec 16, 2015].
2. Cesar C, Shepherd BE, Krollewiecki AJ, Fink VI, Schechter M, Tuboi SH, et al. Rates and reasons for early change of first HAART in HIV-1-infected in 7 sites throughout the Caribbean and Latin America. PLoS One. 2010;5(1):10490.
3. Fangel SJ. The effectiveness of highly active antiretroviral therapy in HIV-infected patients. Dan Med Bull. 2004;51:371–92.
4. Fellay J, Boubaker K, Ledergerber B, Bernasconi E, Furrer H, Battegay M, et al. Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV cohort study. Lancet. 2001;358(9290):1322–7.
5. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239–45.
6. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992;49:2229–32.
7. Rawlins MD, Thompson JW. Mechanism of adverse drug reaction. In: Davies DM (Ed.), *Textbook of Adverse Drug Reactions*, 4th edn. Oxford: Oxford Medical Publication, 1991.
8. Srikanth BA, Babu SC, Yadav HN, Jain SK. Incidence of adverse drug reactions in human immune deficiency virus-positive patients using highly active antiretroviral therapy. J Adv Pharm Technol Res. 2012;3(1):62–7.
9. Lartey M, Quashie AA, Essel A, Kenu E, Ganu V, Neequaye A. Adverse drug reactions to antiretroviral therapy during the early art period at a tertiary hospital in Ghana. Pan Afr Med J. 2014;18:25.
10. Jha AK, Gadgade A, Shenoy AK, Chowta MN, Ramapuram JT. Evaluation of adverse drug reaction in HIV positive patients in a tertiary care hospital. Perspect Clin Res. 2015;6(1):34–6.
11. Maniar NG, Desai S. Antiretroviral therapy: real challenges for developing world. AIDS. 2000;14(4):86.
12. Millogo A, Lankoande D, Yameogo I, Yaméogo AA, Sawadogo AB. Polyneuropathies in patients treated with HAART in Bobo-Dioulasso hospital, Burkina Faso. Bull Soc Pathol Exot. 2008; 101:11–3.
13. Montessori V, Press N, Harris M, Akagi L, Montaner JSG. Adverse effects of antiretroviral therapy for HIV infection. CMAJ. 2004; 170(2).
14. Nadkar MY, Bajpai S. Antiretroviral therapy: toxicity and adherence. J Assoc Physicians India. 2009;57(5):375–6.
15. Ogundahunsi OA, Oyegungle VA, Ogun SA, Odusoga OL, Daniel OJ. HAART and lipid metabolism in a resource poor West African setting. Afr J Biomed Res. 2008;11:27–31.
16. Patel AK, Pujari S, Patel K, Patel J, Shah N, Patel B, et al. Nevirapine versus efavirenz based antiretroviral treatment in naïve Indian patients: comparison of effectiveness in clinical cohort. JAPI. 2006;54:915–8.
17. Salami AK, Olatunji PO, Fawibe EA, Oluboyo PO. Influence of highly active antiretroviral therapy (HAART) on the survival of HIV-infected patients: part report of the ilorin trial centre. Afr J Clin Experimen Microbiol. 2005;6:34–9.
18. Sharma A, Vora R, Modi M, Sharma A, Marfati Y. Adverse effects of antiretroviral treatment. Indian J Dermatol Venereol Leprol. 2008;74(3):234–7.
19. Singh H, Dulhani N, Tiwari P, Singh P, Sinha T. A prospective, observational cohort study to elicit adverse effects of antiretroviral agents in a remote resource-restricted tribal population of Chhattisgarh. Indian J Pharmacol. 2009;41(5):224–6.
20. Seth P .The situation of HIV/M.*tuberculosis* co-infection in India. Open Infect Dis J. 2011;5(1–5):51–9.
21. Heil EL, Townsend ML, Shipp K, Clarke A, Johnson MD. Incidence of severe hepatotoxicity related to antiretroviral therapy in HIV/HCV coinfected patients. AIDS Res Treat 2010; article ID 856542.
22. Reliquet V, Mussini JM, Chennebault JM, Lafeuillade A, Raffi F. Peripheral neuropathy during Stavudine–Didanosine antiretroviral therapy. HIV Med. 2001;2(2):92–6.
23. Radhakrishnan R, Vidyasagar S, Varma M, Naik A, Hegde MB, Guddattu V, Kamath A. Pattern of use of highly active antiretroviral therapy regimens and pattern of occurrence of adverse drug reactions in an Indian human immunodeficiency virus positive patients. Clin Res HIV Aids Prevention. 2013;1(3):1–12.
24. Reddy AVK, Lihite RJ, Lahkar M, Choudhury U, Baruah SK. A study on adverse drug reactions in HIV infected patients at a art centre of tertiary care hospital in Guwahati, India. Asian J Pharm Clin Res. 2013;6(2):102–4.

How to cite this article: Sadiq S, Gupta S, Khajuria V, Tandon VR, Mahajan A, Gupta M. Adverse drug events due to Antiretroviral Therapy in a Northern Indian Tertiary Care Institution. Natl J Physiol Pharm Pharmacol 2016;6:205-208

Source of Support: Nil, **Conflict of Interest:** None declared.