Evaluation of Direct Cost of Adverse Drug Reactions to Highly Active Antiretroviral Therapy in Indian Human Immunodeficiency Virus Positive Patients

Radhakrishnan Rajesh**, Sudha Vidyasagar³, Danturulu Muralidhar Varma², Noorunnisa⁴, Vasudeva Guddattu⁶

¹Manipur College of Pharmaceutical Sciences, Manipal University, Manipal – 576 104, Karnataka, India.
²Kasturba Medical College, Manipal University, Manipal – 576 104, Karnataka, India.
³Indegene Lifesystems, Bangalore – 560 071, Karnataka, India.
⁴Department of Statistics, Manipal University, Manipal – 576 104, Karnataka, India.

ABSTRACT

In India, interruptions to highly active antiretroviral therapy (HAART) are due to adverse drug reactions (ADRs) and no reports on the direct cost incurred in the management of ADRs to HAART are available. There is a need to study direct cost incurred with ADRs to HAART to explore the high economic cost burden imposed by ADRs to HAART in HIV/AIDS patients. This study was aimed to evaluate the direct cost incurred in the management of ADRs to HAART in Indian HIV positive patients. This prospective study was conducted at a Medicine department in a South Indian tertiary care teaching hospitals where ADRs reporting system exist. HIV-positive hospitalized in-patients were identified and intensively monitored for ADRs to HAART. The World Health Organization (WHO) probability scale was used for causality assessment of ADRs. Modified Hart wig and Siegel scale was used for severity assessment of ADRs. Pearson chi-square test identified association of mean direct cost between ADRs and without ADRs by investigating total mean direct cost. The overall direct cost per ADRs to HAART was found to be higher in the context of expenditure on health care cost in India.

Corresponding author: E-mail: rrajes3775@gmail.com, rrajes3775@hotmail.com

Running title: Highly active antiretroviral therapy and direct cost of adverse drug reactions

Key Words: Human immunodeficiency virus; direct cost; hospitalized patients; adverse drug reaction; highly active antiretroviral therapy.
**Introduction**

Human immunodeficiency virus (HIV) infected patients requires a combination of three to four antiretroviral, termed highly active antiretroviral therapy (HAART). HIV infected patients with HAART have a higher risk of developing adverse drug reactions (ADRs) than the general population and have a significant impact on patient’s current and future care options. ADRs to HAART are recognized as the key factor that increases the overall healthcare costs in both admission to hospital and prolongation of length of hospital stay. ADRs to HAART are one of the leading causes that affects the quality of life in HIV/Acquired immunodeficiency syndrome (AIDS) and results in increase in direct and indirect cost of HIV management with economic burden to the HIV infected patients as well as to the society. In India, the National AIDS Control organization (NACO) initiated free HAART for HIV and related opportunistic infections. Currently, over 320,000 people living with HIV receiving HAART at more than 260 public government hospitals across the country. According to NACO treatment, HIV infected patients receive a fixed dose HAART regimen, consisting of either zidovudine or stavudine with lamivudine in combination with either efavirenz or nevirapine. In India, 25% of HIV patients discontinue their initial HAART regimen within the first eight months of therapy because of ADRs which leads to noncompliance. Studies have assessed the direct cost of ADRs at different hospitals using length of stay as a parameter for evaluation. Recent study suggest that indirect cost such as disability, work productivity losses related to absenteeism and other financial cost was also associated in the management of HIV/AIDS. The evaluation of indirect cost associated from ADRs is rare and is found in only very few studies. The cost analysis of ADRs in HIV infected patients depends upon different HAART regimen based on the patient’s viral load as well as individual level of HIV/AIDS care. In an Australian study 5.7% of all admissions were drug related, out of which 4.9% were due to ADRs, resulted in a calculated cost of > € 2 million, or €3077 per patient. Study Conducted in Germany estimated direct cost associated with ADRs ranged from 0.4 billion dollars annually. In United States study revealed that the cost of ADRs per patient was in the range of US$2000 to US$4000. Wasserfallen et al. showed that a mean length of stay of nine days in a hospital attributes to ADRs resulting in a cost of €3122 per ADR. Moore et al. showed that the average cost of ADRs was estimated to be €2900 and Lagnaoui et al. showed that the mean cost of ADRs € 2700 per patient in a department of internal medicine. In India, Ramesh et al. estimated cost associated in treating all reported ADRs was US$ 1595, with average US$ 15 per ADR. Thiyagu et al. study from India showed that total cost incurred due to ADRs in a tertiary care teaching hospital was found to be US$ 36451 with average US$ 115 per patient hospitalized with ADRs. The aim of this work was to evaluate the direct cost incurred in the management of ADRs to HAART in Indian HIV positive patients.

**Materials and Methods**

A prospective observational study was conducted from March 2010 to February 2011 among HIV-infected hospitalized in-patients by a clinical pharmacist at the medicine department in a teaching hospital where ADR reporting system exists. The study was approved by the institutional ethics committee. HIV-infected hospitalized in-patients of either sex who were on fixed dose drug combinations of HAART were included in the study and HIV positive patients with Systemic Lupus Erythmatosus (SLE), cancer, pregnant women and patients with traditional medicines were excluded from the study. Patients were divided into two groups. The first group with presence of ADRs to HAART regimen (Cases) and second group with absence of ADRs to HAART regimen (Controls). Based on the study criteria, the study procedure was explained and written informed consent was obtained from these patients. For the study purposes World health organization (WHO) definition of an ADR was adopted.

During the study period, hospitalized in-patients was intensively monitored for short term and long term ADRs to HAART by active follow-up after treatment and ADRs was detected by asking patients directly and by screening patients medical case records. The occurrence of ADRs to HAART was documented with details of suspected HAART involved for ADRs; treatment given for ADRs was documented using ADR documentation forms. Documented ADRs was reviewed and assessed by senior clinical pharmacist and was reported to the treating clinicians and affected HIV patients. WHO probability scale was used for the causality assessment of ADRs. The severity of suspected ADRs was assessed using the modified Hart wig and Siegel scale.

Evaluation of actual direct cost with ADRs and without ADRs to HAART was based on the cost of treatment, cost of hospitalization stay, and cost of laboratory investigations in comparison to a “normal” length of stay without ADR. In cases of ADR causing a hospital admission, all hospital costs to the ADR was calculated, as the patient would not have been hospitalized without the ADR i.e. length of stay multiplied by costs per patient per day. Assessment of ADR that leads to increase in the length of stay was performed after physician’s judgement. Billing details was collected from computerized Hospital In-Patients Billing System (HIPBS). The cost of treatment that includes, all costs of medications, surgical supply such as syringes, professional charges, nursing care charges, administrative charges. The cost of laboratory investigations that includes all costs of clinical laboratory investigation (Continued on page 14)
charges and any other invasive or noninvasive additional procedures performed. The cost of hospitalization charges includes cost of ward charges, bed charges and hospital stay charges. The data observed was analyzed in order to study the total mean direct cost versus mean direct cost per ADRs.

**Statistical Analysis**

Patients who presented with ADRs to HAART (Cases) and those who had not experienced with ADR to HAART (Controls) were compared with Chi-square test for gender, age and CD4 Count. Frequencies with percentage were used to represent gender, age, CD4 count, HAART regimen implicated, occurrence of ADRs and severity of ADRs to HAART. The association between direct cost incurred due to ADRs in HIV positive patients receiving HAART were determined at a P value <0.05 by investigating mean cost of treatment, mean cost of laboratory investigations and mean cost of hospitalization stay charges. (Minimum, maximum), Median and Chi-square test was used to evaluate the direct cost incurred to ADRs to HAART. All statistical calculations were performed using Statistical Package for Social Science (SPSS), version 17.0. A P value of <0.05 was considered as statistically significant.

**Results**

A total of 110 HIV positive patients (84 males and 26 females) with HAART were admitted to the hospital during the study period. Out of which 56 patients (42 males and 14 females) experienced ADRs to HAART i.e. (Cases) and 54 patients was not experienced with ADRs to HAART i.e. (Control). A total of 57.2% of HIV positive hospitalized in-patients experienced ADRs to HAART and 41.1% of ADRs to HAART were related to hospital admissions. ADRs were highest with zidovudine + lamivudine+ nevirapine (35.5%) and lamivudine + stavudine + nevirapine (17.9%) combinations. CD4 cell count in patients with ADRs to HAART was ≤ 200 cells/μl. Pearson chi-square test showed statistical significant difference of mean direct cost incurred among age group between cases and control (p=0.021 i.e. p<0.05). The total cost incurred in managing ADRs to HAART was highest with tenofovir + emtricitabine + lopinavir + ritonavir combination, INR 21822.4 (US$ 474.4) and lamivudine + stavudine + tenofovir combination, INR 17521.4 (US$ 380.9). Mean direct cost incurred in treating per ADR in hospitalized patients with HAART ranges from INR 524.4 (US$ 11.4) to INR 17521.4 (US$ 380.9), as presented in Table 2.

The total direct cost of treating ADRs to HAART was highest with tenofovir + emtricitabine + lopinavir + ritonavir combination, INR 21822.4 (US$ 474.4) and lamivudine + stavudine + tenofovir combination, INR 17521.4 (US$ 380.9). Mean direct cost incurred in treating per ADR in hospitalized patients with HAART was INR 3549 (US$ 77.15), INR 39926 (US$ 867.95) and INR 28953 (US$ 629.41) respectively. The cost of management of ADRs to HAART based on the severity was summarized in Table 4.

In our study the direct cost incurred in managing ADRs to HAART reported was INR 72428 (US$ 1574.51). The cost incurred in treating each ‘mild’, ‘moderate’ and ‘severe’ ADRs to HAART was INR 3549 (US$ 77.15), INR 39926 (US$ 867.95) and INR 28953 (US$ 629.41) respectively. The cost of management of ADRs to HAART based on the severity was summarized in Table 5.

In our study, the overall incidence of ADRs to HAART was determined using Pearson chi-square test by investigating the mean cost of treatment (p=0.004 i.e. p<0.05), the mean cost of laboratory investigations (p=0.001 i.e. p<0.05) and mean cost of hospitalization stay (p=0.003 i.e. p<0.05). Results are summarized in Table 2.

The total direct cost of treating ADRs to HAART was highest with tenofovir + emtricitabine + lopinavir + ritonavir combination, INR 21822.4 (US$ 474.4) and lamivudine + stavudine + tenofovir combination, INR 17521.4 (US$ 380.9). Mean direct cost incurred in treating per ADR in hospitalized patients with HAART ranges from INR 524.4 (US$ 11.4) to INR 17521.4 (US$ 380.9), as presented in Table 3.
reactions to antiretroviral therapy in HIV positive patients at Kasturba hospital Manipal. *BMC Infectious Disease*, 2012; 12 (Suppl 1): P55.

2. Thiyagu R, Surulivelrajan M, Vasudeva G, Asha K, Rajesh V, Padma GM, Laxminarayana KB. Cost of adverse drug reaction in a south Indian tertiary care teaching hospital. *Journal of clinical pharmacology*, 2012; 52:559-565.

3. Dodds C, Colman R, Amaratunga C, Wilson J. The cost of HIV/AIDS in Canada. Genuine progress index. http://www.gpiatlantic.org/pdf/health/costofaids.pdf. Accessed January 2010.

4. National AIDS Control organization. *Country progress report: UNGASS*. India 2010. New Delhi, India; 2010 (cited 21 September 2010). Available at: http://unaidsonline.org/en/knowledgecentre/hivdata/countryprogress/2010CountryProgressAllCountries.asp. Accessed September 21, 2010.

5. Ministry of health and family welfare government of India. *Antiretroviral therapy guidelines for HIV-Infected Adults and Adolescents including post-exposure prophylaxis*. New Delhi, India: National AIDS Control organization; 2007.

6. Rajesh R, Vidyasagar S, Varma DM, Mohiuddin S, Norrunnisa. Evaluation of incidence of zidovudine induced anemia in Indian human immunodeficiency virus positive patients in comparison with stavudine based highly active antiretroviral therapy. Jt J Risk Saf Med. 2011; 23 (3):171-180.

7. Goettler M, Schneewess S, Hasford J. adverse drug reaction monitoring-cost and benefit consideration part II: cost and preventability of adverse drug reactions leading to hospital admission. *Pharmacoepidemiol Drug Safety*, 1997; 6: 579-590.

8. Dukes MN. Economic costs of adverse drug reactions. *Pharmacoeconomics*, 1992; 1(3):153-154.

9. Eisenberg JM. Clinical economics. A guide to the economic analysis of clinical practice. *JAMA*, 1989; 262(20):2879-2886.

10. Senst BL, Achesim LE, Genest RP. Practical approach to determining costs and frequency of adverse drug events in a healthcare network. *American Journal of Health system pharmacist*, 2001; 58:1126-1132.

11. Hutchinson AB, Farnham PG, Dean HD. The economic burden of HIV in the United States in the era of highly antiretroviral therapy: Evidence of continuing racial and ethnic differences. *J Acquir Immune Defic Syndr*. 2006; 43:451–475.

12. Bates DW, Spell N, Cullen DJ. The cost of adverse drug events in hospitalized patients. *JAMA*. 1997; 277(4):307-311.

13. Simpson KN, Jones WJ, Rajagopalan R, Dietz B. Cost effectiveness of lopinavir/ritonavir tablets compared with atazanavir plus ritonavir in antiretroviral-experienced patients in the UK, France, Italy and Spain. *Clin Drug Invest*. 2007; 27:807-817.

14. Panel on Antiretroviral Guidelines for Adults and Adolescents, Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed January 2010.

15. AIDS Study Group. Recommendations of National Plan on AIDS: Antiretroviral treatment of HIV-infected adults (January 2008 update) [in Spanish]. http://www.gesida.seimc.org. Accessed January 2010.

16. Harris M, Montaner JS. Management of HIV-infected patients with multidrug-resistant virus. *Curr HIV/AIDS Rep*. 2004; 1:116–121.

17. Dartnell JGA, Anderson RP, Chohan V. Hospitalisation for adverse events related to drug therapy: incidence, availability and costs. *Med J Aust.* 1996; 164:659-662.

18. Schneeewiss S, Hasford J, Gottler M, Hoffmann A, Riethling AK, Avorn J. Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study. *Eur J Clin Pharmacol*. 2002; 58: 285-291.

19. Bordet R, Gautier S, Le Louet H, Dupuis B. Caron J. Analysis of the direct cost of adverse drug reactions in hospitalized patients. *Eur J Clin Pharmacol*. 2001; 56:935-841.

20. Wasserfallen JB, Livio F, Buclin T, Tillet L, Yersin B, Biollaz J. Rate type, and cost of adverse drug reactions in emergency department admissions. *Eur J Intern Med.* 2001; 12:442-44.

21. Moore N, Lecointre D, Noblet C, Mabille M. Frequency and cost of serious adverse drug reactions in a department of general medicine. *Br J Clin Pharmacol*. 1998; 45:301-308.

22. Lagnauol R, Moore N, Fach J, Longy- Boursier M, Begaud B. Adverse drug reaction in a department of systemic disease-oriented internal medicine: prevalence, incidence, direct costs and avoidability. *Eur J Clin Pharmacol*. 2000; 55:181-186.

(Continued on page 21)
### Table 1. Demographic Characteristic of the patients

| Patient Characteristics | Number of Patients (%) | Mean direct cost | p-Value |
|-------------------------|------------------------|-----------------|---------|
| ADR present (Cases)     | ADR absent (Control)   | Number of patients (n=110) | With ADR (Cases) | Without ADR (Control) |
|                         |                        |                 | INR | US$ | INR | US$ |
| Gender                  |                        |                 |     |     |     |     |
| Male                    | 42(75)                 | 42(77.8)        | 84(76.4) | 3818 | 83 | 1430.6  | 31.1 | 0.732 |
| Female                  | 14(25)                 | 12(22.2)        | 26(23.6) | 4719.6 | 102.6 | 1205.2  | 26.2 |
| Age (years)             |                        |                 |     |     |     |     |
| 18-40                   | 29(51.8)               | 20(37)          | 49(44.5) | 5391.2  | 117.2 | 984.4  | 21.4 | 0.021 |
| 41-60                   | 23(41)                 | 34(63)          | 57(51.9) | 2714 | 59 | 1614.6  | 35.1 |
| ≥ 60                    | 4 (7.2)                | 4(3.6)          | 1904.4 | 41.4 |
| CD4 Count (Cells/µl)   |                        |                 |     |     |     |     |
| ≤ 200                   | 44(78.6)               | 43(79.6)        | 87(79) |     |     |     |     |
| >200                    | 12 (21.4)              | 11(20.4)        | 23(21) |     |     |     |
| HAART regimen implicated |                        |                 |     |     |     |     |
| Zidovudine+Lamivudine+Nevirapine | 20 (35.7)   | 15 (27.8)       | 35(31.8) |     |     |     |     |
| Lamivudine+Stavudine+Nevirapine | 10 (17.9)    | 5(9.3)          | 15(13.6) |     |     |     |     |
| Tenofovir+Emtricitabine+Efavirenz | 9 (16.1)    | 22(40.7)       | 31(28.2) |     |     |     |     |
| Zidovudine+Lamivudine+Efavirenz | 7 (12.5)     | 6(11.1)         | 13(11.8) |     |     |     |     |
| Lamivudine+Stavudine+Efavirenz | 6 (10.7)     | 5(9.3)          | 11(10.1) |     |     |     |     |
| Lamivudine+Stavudine+Tenofovir | 1 (1.8)      | 1(0.9)          |     |     |     |     |
| Tenofovir+Emtricitabine+Lopinavir | 3 (5.3)     | 1 (1.8)         | 4(3.6) |     |     |     |     |
| Occurrence of ADRs      |                        |                 |     |     |     |     |
| ADRs during hospital stay | 32 (57.2)  |     |     |     |     |     |
| ADR is the reason for hospital ad- | 23(41.1)    |     |     |     |     |     |
| Re occurrence of exposure of ADRs | 1(1.7)      |     |     |     |     |     |

1US$ = 46 INR (Indian Rupees)

p- Value of <0.05 was considered as statistically significant by pearson chi-square test.
### No of ADRs

| Highly active antiretroviral therapy | Mean direct cost |
|-------------------------------------|------------------|
|                                     | Mean cost of treatment (INR, US$) | Mean cost of Hospitalization stay (INR, US$) | Mean cost of lab investigations (INR, US$) | Total mean direct cost (INR, US$) | Mean cost per ADR (INR, US$) |
|-------------------------------------|------------------|
| Zidovudine + Lamivudine + Nevirapine | 20               | 5276.2, 114.7 | 3302.8, 71.8 | 1932, 42 | 10511, 228.5 | 524.4, 11.4 |
| Lamivudine + Stavudine + Nevirapine | 10               | 1756.2, 38.18 | 2750.8, 59.8 | 1610, 35 | 6117, 132.8 | 607.2, 13.2 |
| Tenofovir + Emtricitabine + Efavirenz | 9                | 3997.4, 86.9 | 3353.4, 72.9 | 3353.4, 72.9 | 10704.2, 232.7 | 1186.8, 25.8 |
| Zidovudine + Lamivudine + Efavirenz | 7                | 2010.2, 43.7 | 3183.2, 69.2 | 1536.4, 33.4 | 6729.8, 146.3 | 961.4, 20.9 |
| Lamivudine + Stavudine + Efavirenz | 6                | 805, 17.5 | 2323, 50.5 | 1748, 38 | 4876, 106 | 809.6, 17.6 |
| Lamivudine + Stavudine + Tenofovir | 1                | 6762, 147 | 6481.4, 140.9 | 4278, 93 | 17521.4, 380.9 | 17521.4, 380.9 |
| Tenofovir + Emtricitabine + Lopinavir + Ritonavir | 3      | 13892, 302 | 5400.4, 117.4 | 2530, 55 | 21822.4, 474.4 | 7268, 158 |
**Table 5.** Cost based on severity of adverse drug reactions in intensively monitored HIV positive patients receiving highly active antiretroviral therapy.

| Severity | Level | No of ADRs n = 56(%) | Cost of management of ADRs to HAART |
|----------|-------|----------------------|------------------------------------|
|          |       |                      | INR | US$     |
| Mild     | Level 1 | 3(5.4)                | 3549 | 77.15   |
|          | Level 2 | 3(5.4)                |      |         |
| Moderate | Level 3 | 1(1.7)                | 39926 | 867.95  |
|          | Level 4 (a) | 18(32.2)               |      |         |
|          | Level 4 (b) | 23(41)                |      |         |
| Severe   | Level 5 | 6(10.9)               | 28953 | 629.41  |
|          | Level 6 | 1(1.7)                |      |         |
|          | Level 7 | 1(1.7)                |      |         |
|          |         |                      | 72428 | 1574.51 |

1US$ = 46 INR (Indian Rupees)

**Figure 1.** Level of severity adverse drug reaction to highly active antiretroviral therapy
Table 4. Cost of some of the most important adverse drug reaction (ADRs) to highly active antiretroviral therapy.

| Adverse drug reactions | No of ADRs n=56 (%) | Mean direct cost of ADRs |
|------------------------|---------------------|-------------------------|
|                        |                     | Mean cost of treatment to ADRs | Mean cost of hospitalization stay due to ADRs | Mean cost of lab investigations due to ADRs | Total mean direct cost | Mean direct cost per ADR |
|                        |                     | INR | US$ | INR | US$ | INR | US$ | INR | US$ | INR | US$ | INR | US$ |
| Zidovudine induced anemia | 15 (26.9) | 5901.8 | 128.3 | 3008.40 | 65.4 | 1784.8 | 38.8 | 10695 | 232.5 | 713 | 15.5 |
| Zidovudine induced nausea & vomiting | 7(12.5) | 1743.4 | 37.9 | 2401.2 | 52.2 | 1858.4 | 40.4 | 6003 | 130.5 | 860.2 | 18.7 |
| Nevirapine and efavirenz induced hepatotoxicity | 7(12.5) | 1504.2 | 32.7 | 2387.4 | 51.9 | 1725 | 37.5 | 5616.6 | 122.1 | 802.7 | 17.45 |
| Stavudine induced peripheral neuropathy | 6(10.8) | 1030.4 | 22.4 | 1646.8 | 35.8 | 1380 | 30 | 4057.2 | 88.2 | 676.2 | 14.7 |
| Stavudine induced pancreatitis | 4(7.1) | 14536 | 316 | 7774 | 169 | 3795 | 82.5 | 26105 | 567.5 | 6527.4 | 141.9 |
| Efavirenz induced skin rash | 3(5.7) | 1886 | 41 | 2815.2 | 61.2 | 1610 | 35 | 6311.2 | 137.2 | 2106.8 | 45.8 |
| Nevirapine induced Stevens Johnson Syndrome (SJS) | 2(3.5) | 10672 | 232 | 6808 | 148 | 1702 | 37 | 19182 | 417 | 9591 | 208.5 |
| Tenofovir induced renal failure | 2(3.5) | 6072 | 132 | 2700.2 | 58.7 | 2341.4 | 50.9 | 11113.6 | 241.6 | 5556.8 | 120.8 |
| Efavirenz induced depression | 2(3.5) | 8004 | 174 | 7452 | 162 | 4351.6 | 94.6 | 19807.6 | 430.6 | 9903.8 | 215.3 |
| Zidovudine and Lamivudine induced pancytopenia | 2(3.5) | 2852 | 62 | 5612 | 122 | 1495 | 32.5 | 9959 | 216.5 | 4981.8 | 108.3 |
| Lopinavir and Ritonavir induced diarrhea | 2(3.5) | 2603.6 | 56.6 | 3657 | 79.5 | 1384.6 | 30.1 | 7645.2 | 166.2 | 3822.6 | 83.1 |
| Efavirenz induced gastritis | 2(3.5) | 1228.2 | 26.7 | 2456.4 | 53.4 | 1771 | 38.5 | 5455.6 | 118.6 | 2727.8 | 59.3 |
| Zidovudine induced fever | 2(3.5) | 294.4 | 6.4 | 2010.2 | 43.7 | 1058 | 23 | 3362.6 | 73.1 | 1683.6 | 36.6 |
DISCUSSION

This is the first study conducted on Indian HIV-infected patients that explores the direct cost incurred in the management of ADRs to HAART. Use of HAART results in a wide range of adverse effects which are expensive to manage leading to morbidity and mortality. In a United States study, it has been shown that ADRs rank fourth to sixth leading cause of death. Various studies concluded that in industrialized countries, ADRs accounts for 5 to 10% of hospital costs. In the present study, we estimated only the direct cost incurred in the management of ADRs to HAART, as indirect cost includes social cost, loss of productivity that are difficult to analyze. Various studies have also analyzed direct cost of ADRs.

Our study revealed male predominance over female. This may be due to the fact that in our study female HIV infected patients refuse for HIV treatment due to social stigma and illiteracy. These observations are in agreement with the previously published study elsewhere. However, in our study mean direct cost incurred in treating ADRs to HAART in female patient was higher compared to males. This may be due to the fact that in our study two female HIV-infected patients presented with nevirapine induced Steven–Johnson Syndrome resulted in increased length of hospital stay of 20 days. This is in accordance with published studies.

The total mean direct cost seems very less in developing country like India, compared to developed countries like United States where the direct cost incurred in treating ADRs to HAART ranges to several thousand dollars. But when compared to economic status of expenditure on health care cost in India, this cost associated with ADRs is significantly high. This is because most of our HIV infected patients were below the poverty line, even unable to afford their daily food and inability to pay for their HAART. This is in accordance with published studies.

In our study, the patient presented with severe renal dysfunction with increased risk of grades 3 to 4 nephrotoxicity due to tenofovir usage, necessitating them to receive multiple dialysis. Thus overall costs leads to higher expenditure from the patients in terms of laboratory investigations to investigate tenofovir induced renal failure; the length of stay in the hospital was prolonged and resulted in escalating the cost of treatment. This finding is in agreement with published studies where the laboratory investigations, length of hospital stay and treatment costs are responsible components for the overall direct cost of management of ADRs.

In the management of stavudine induced pancreatitis costs incurred was due to laboratory investigations such as lipase measurement, serum amylase and imaging studies. Three patients in our study with stavudine induced pancreatitis also developed sepsis with systemic inflammatory response syndrome and multiple organ failure. The offending drug stavudine was withdrawn and patient was on supportive measures of intravenous fluid administration, complete bed rest in the hospital for 10 days. which leads to higher expenditure of direct cost. A finding consistent with the study carried out by Moore et al.

Efavirenz induced severe depression developed psychiatric symptoms with aggressive behavior with nonfatal suicide attempts, insomnia, irritability, suicidal ideation, impaired concentration, vivid dreams, and paranoid reactions and manic reactions. The patient’s length of stay in the hospital was prolonged for more than 20 days which resulted in higher cost burden associated with ADRs to HAART. These observations are in agreement with published study.

In our study the cost of management of nevirapine induced Steven–Johnson Syndrome (SJS) includes supportive measures with antimicrobial therapy, extra skin care, intravenous fluid administration, electrolyte maintenance cost and increased in the length of hospital stay in intensive medical care resulted in greater expenditure to the patient. One case of SJS with Level 7 severity which led to the death of the patient. This finding reflects the cost burden of ADRs to HAART. This is in accordance with published studies.

**Conclusion**

The overall direct cost associated in treating ADRs to HAART was found to be higher and significantly represents that ADRs to HAART increases the overall health care cost in the management of HIV/AIDS as well as reflects high economic burden to HIV/AIDS patients. I Clinicians and pharmacist must focus to prevent early ADRs to HAART thereby decreasing ADR related costs.

**Competing Interests**

The authors declare no conflicts of interest.

**References**

1. Poornima P, Rajesh R, Sudha V, Varma DM. Assessment of hematological adverse drug
23. Ramesh M, Pandit J, Parthasarathi G. Adverse drug reactions in a south Indian hospital-their severity and cost involved. Pharmacoepidemiol Drug Saf 2003; 12:687-692.

24. Modayil R, Anand H, Parthasarathi G, Ramesh M, Vasudeva N. Adverse drug reactions to antiretroviral therapy (ART): an experience of spontaneous reporting and intensive monitoring from ART centre in India. Pharmacoepidemiol Drug Saf 2010; 19 (3): 247-255.

25. World Health Organization. Technical Report Series 498 World Health Organization: Geneva, 1972.

26. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis and management. Lancet. 2000:356:1255-1259.

27. World Health Organization. Uppsala Monitoring Center. Safety monitoring of medicinal products, guidelines for setting up and running pharmacovigilance center, Geneva 1996. Available at: URL: http://www.who.int/en/ (accessed 25 January 2011).

28. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992; 49:2229-32.

29. Suh DC, Woodall BS, Shin SK, Hermes DE. Clinical and economic impact of adverse drug reactions in hospitalized patients. Ann Pharmacother.2000:34:1373-1379.

30. Lazarou J. Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998; 279(15):1200-1205.

31. Detournay B, Fagnani F, Pouyanne P. Cost of hospitalizations for adverse drug reaction related hospitalizations -cost of to side effects of drugs [Cmft des hospitalisations pour effet indesirable medicamenteux]. Therapy. 2000; 55:137-139.

32. Chen RY, Accortt NA, Westfall AO. Distribution of health care expenditures for HIV-infected patients. Clin Infect Dis. 2006; 42:1003–1010.

33. Lobas NH, Lepinski PW, Abramowitz PW. Effects of Pharmaceutical care on medication cost and quality of patient care in an ambulatory care clinic. Am J Hosp Pharm. 1992; 49:1681-1688.

34. White TJ, Arakelian A, Rho JP. Counting the costs of drug-related adverse events. Pharmacoeconomics. 1999; 15(5):445-458.

35. National Center of Epidemiology. Carlos III Institute of Health. Monograph: HIV and AIDS in Spain. Epidemiologic status, 2001. Chapter 2: Epidemiologic monitoring of AIDS [in Spanish].

http://www.isciii.es/htdocs/centros/epidemiologia/epi_descarga_libro.jsp. Accessed January 2010.

36. Moore N, Lecointre D, Noblet C, Mabille M. Frequency and cost of serious adverse drug reactions in a department of general medicine. 1998; 45:301-308.

37. Blitz M, Spivack E, Kerpel S, Freedman P. Stevens-Johnson syndrome in an HIV infected patient. AIDS Read. 1999; 9:184–185,190.

38. Kumarasamy N, Safren SA, Raminani SR. Barriers and facilitators to antiretroviral medication adherence among patients with HIV in Chennai, India: A qualitative study. AIDS Patient Care STDS 2005; 19:526-37.

39. Tribino G, Maldonado C, Segura O, Dfaz J. Direct costs and clinical aspects of adverse drug reactions in patients admitted to a level three hospital internal medicine ward. Biomedica. 2006; 26:31-41.

40. Moore RD, Keruly JC, Chaisson RE. Incidence of pancreatitis in HIV-infected patients receiving nucleoside reverse transcriptase inhibitor drugs. AIDS 2001; 15: 617-20.

41. Jordi B, Esteban M, Araceli R, Jose LB, Miguel AG, Josep MP, Elisa DL. Preliminary data of a prospective study on neuropsychiatric side effects after initiation of efavirenz. J Acquir Immune Defic Syndr. 2001; 27:336–343.

42. Jean PF, Maja M, Jan CR. Nevirapine and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. Clin Infect Dis. 2001; 27:325–330.

43. Moore RD. Cost effectiveness of combination HIV therapy: 3 years later. Pharmacoeconomics 2000; 17:235-30.

44. Hellinger FJ, Fleishman JA. Estimating the national cost of treating people with HIV disease: patient, payer, and provider data. J Acquir Immune Defic Syndr 2000; 24:182-8.

(Continued on page 16)