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Research Article

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

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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 hospital where an ADRs reporting system exists. 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.

Keywords:
Human immunodeficiency virus; direct cost; hospitalized patients; adverse drug reaction; highly active antiretroviral therapy

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Introduction

Human immunodeficiency virus (HIV) infected patients requires a combination of three to four anti-retrovirals, 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. [1] 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. [2] ADRs to HAART are one of the leading causes that affect the quality of life in HIV/Acquired immunodeficiency syndrome(AIDS) and result in an increase in direct and indirect cost of HIV management with economic burden to the HIV infected patients as well as to the society. [3] In India, the National AIDS Control organization (NACO) initiated free HAART for HIV and related opportunistic infections [4]. Currently, over 320,000 people living with HIV are 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. [5] 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. [6] Studies [7], [8], [9], [10] have assessed the direct cost of ADRs at different hospitals using length of stay as a parameter for evaluation. A recent study [11] suggests 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 [12]. 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. [13], [14], [15], [16] In an Australian study 5.7% of all admissions were drug related, out of which 4.9% were due to ADRs, resulting in a calculated cost of > € 2 million, or €3077 per patient. [17] Study Conducted in Germany estimated direct cost associated with ADRs ranged from 0.4 billion dollars annually. [18] A United States study [19] revealed that the cost of ADRs per patient was in the range of US$2000 to US$4000. Wasserfallen *et al* [20] showed that a mean length of stay of nine days in a hospital attributes to ADRs resulting in a cost of €3122 per ADR. Moore *et al* [21] showed that the average cost of ADRs was estimated to be €2900 and Lagnaoui *et al* [22] showed that the mean cost of ADRs was € 2700 per patient in a department of internal medicine. In India, Ramesh *et al* [23], [24] estimated cost associated in treating all reported ADRs was US$ 1595, with average US$ 15 per ADR. Thiyagu *et al* [2] 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 an 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 [25], [26]

During the study period, hospitalized in-patients were intensively monitored for short term and long term ADRs to HAART by active follow-up after treatment and ADRs were 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 were reviewed and assessed by a senior clinical pharmacist and were reported to the treating clinicians and affected HIV patients. WHO probability scale was used for the causality assessment of ADRs. [27] The severity of suspected ADRs was assessed using the modified Hart wig and Siegel scale. [28]

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. [29] In cases of ADR causing a hospital admission, all hospital costs to the ADR were calculated, as the patient would not have been hospitalized without the ADR i.e. length of stay multiplied by costs per in-patient per day. Assessment of ADR that leads to increase in the length of stay was performed after physician's judgement. Billing details were collected from computerized Hospital In-Patients Billing System (HIPBS). The cost of treatment includes all costs of medications, surgical supplies such as syringes, professional charges, nursing care charges, administrative charges. The cost of laboratory investigations includes all costs of clinical laboratory investigation 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 was 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 statistically 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 among age group 18-40 years INR 5391.2 (US$ 117.2) and 41-60 years INR 2714 (US$ 59). Demographic Characteristic of the patients is shown in Table 1.

Table 1. Demographic Characteristic of the patients

Patient Characteristics	Number of Patients (%)			Mean direct cost				p-Value
	ADR present(Cases) (n= 56)	ADR absent(Control) (n= 54)	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)					0.891
>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)					

Table 1 (continued)

Patient Characteristics	Number of Patients (%)			Mean direct cost				p-Value
	ADR present(Cases) (n= 56)	ADR absent(Control) (n= 54)	Number of patients(n= 110)	With ADR (Cases)		Without ADR (Control)		
				INR	US$	INR	US$	
Tenofovir+Emtricitabine+Lopinavir+ Ritonavir	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 admission	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.

The direct cost incurred between cases (with ADR) and control (without ADR) was based on mean cost of treatment, mean cost of laboratory investigations and mean cost of hospitalization stay. It was identified that mean cost of treatment significantly contributed to the overall direct cost incurred between cases, INR 8556 (US$ 186) and control, INR 2645 (US$ 57.5). The mean cost of laboratory investigations with an ADR to HAART per patient was INR 1913.6(US$ 41.6). The mean cost of hospitalization stay with an ADR to HAART per patient was INR 3261.4(US$ 70.9). The median length of hospital stay with patients with ADRs to HAART was 10 days (range of 10 to 25 days) whereas median length of hospital stay with HIV patients without ADRs to HAART was 4 days (range of 4 to 6 days). The association of direct cost incurred between cases (with ADR) and control (without ADR) in HIV positive patients receiving 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.

The cost of ADRs was studied based on the reported adverse reaction to HAART. In our study stavudine induced pancreatitis that led to the highest cost of management INR 26105 (US$ 567.5) followed by efavirenz induced depression INR 19807.6 (US$ 430.6) followed by nevirapine induced Steven Johnson Syndrome (SJS) INR19182 (US$ 417), tenofovir induced renal failure INR 11113.6 (US$ 241.6) and zidovudine induced anemia INR 10695 (US$ 232.5). The ADRs that led to the lowest cost for management were reported with zidovudine induced fever INR 3362.6 (US$ 73.1) followed by stavudine induced peripheral neuropathy INR 4057.2 (US$ 88.2). The total direct costs of some of the important ADRs to HAART are 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

Table 2. Components of charges incurred in cases and control in intensively monitored HIV positive patients receiving highly active antiretroviral therapy.

Mean direct cost	Number of patients (n =110) p-value								
	ADR present (Cases) (n= 56)				ADR absent (Control) (n= 54)				
	INR	US$	(Min,Max)	Median(Q1, Q3)	INR	US$	(Min,Max)	Median(Q1,Q3)	
Mean cost of treatment	8556	186	(138,53833)	1583.5(736,3329)	2645	57.5	(172,6081)	807(534,1758)	0.004
Mean cost of laboratory investigations	1913.6	41.6	(535,6445)	1650 (1225,2250)	1168.4	25.4	(230,2835)	992(875,1326)	p<0.001
Mean cost of hospitalization stay	3261.4	70.9	(0,12150)	2590(1450,3743)	1927.4	41.9	(629,3780)	1672.5(1353,2322)	0.003

ADR, adverse drug reaction
Min= Minimum, Max= Maximum
Median = (50th percentile)
Q1 = Lower or first quartile (25th percentile)
Q3= Upper or third quartile (75th percentile)
1US$ = 46 INR (Indian Rupees)
p- value of <0.05 was considered as statistically significant

3549 (US$ 77.15), INR 39926 (US$ 867.95) and INR 28953 (US$ 629.41) respectively. The cost of

Table 3. Direct cost of adverse drug reactions (ADRs) involved in highly active antiretroviral therapy.

Highly active antiretroviral therapy	No of ADRs(n= 56)	Mean direct cost									
		Mean cost of treatment		Mean cost of Hospitalization stay		Mean cost of lab investigations		Total mean direct cost		Mean cost per ADR	
		INR	US$	INR	US$	INR	US$	INR	US$	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	132.98	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

1US$ = 46 INR (Indian Rupees)

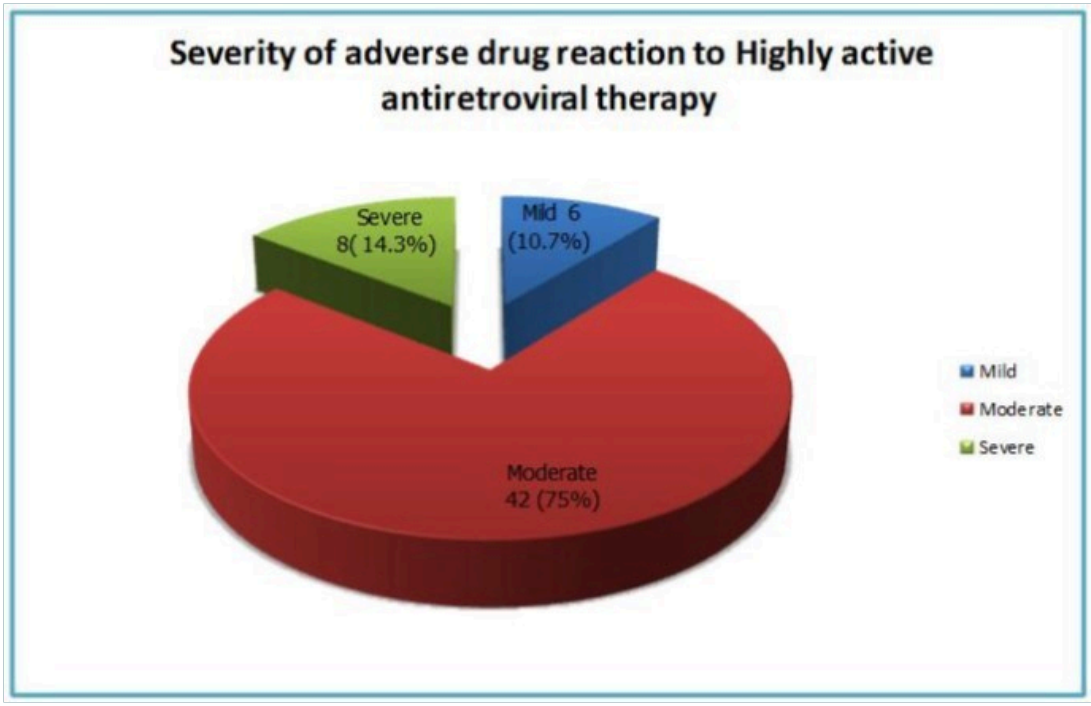


Figure 1. Level of severity adverse drug reaction to highly active antiretroviral therapy

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 found to be 50.9%. In the majority of ADRs to HAART, causality assessment was 'probable' and 'possible' by WHO probability scale. Out of 56 ADRs to HAART, level of severity as per modified Hart wig and Siegel scale [28] accounted for 'mild 6(10.7%)', 'moderate 42(75%)' and 'severe 8(14.3%)'. Results are shown in Figure 1.

Table 4. Cost of some of the most important adverse drug reactions (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$
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

Table 4 (continued)

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$
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

1US$ = 46 INR (Indian Rupees)

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 [30], it has been shown that ADRs rank from the fourth to sixth leading cause of death. Various studies [31], [32] concluded that in industrialized countries, ADRs account 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 [33], [34] 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 [35]. However, in our study mean direct cost incurred in treating ADRs to HAART in female patients was higher compared to males. This may

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)

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. [36], [37]

The total mean direct cost seems very less in a developing country like India, compared to developed countries like the United States where the direct cost incurred in treating ADRs to HAART ranges to several thousand dollars. [19], [20] 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. [38]

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 dialyses. Thus overall costs lead 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 [19], [20], [39] 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. [40]

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. [41]

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 led to the death of the patient. This finding reflects the cost burden of ADRs to HAART. This is in accordance with published studies. [42], [43], [44]

Conclusion

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

Competing Interests

The authors have declared that no competing interests exist.

References

1. Poornima P, Rajesh R, Sudha V, Varma D M. *Assessment of hematological adverse drug reactions to antiretroviral therapy in HIV positive patients at Kasturba hospital Manipal. BMC Infectious Disease.12(Suppl 1)*. 2012:55.
2. Thiyagu R, Surulivelrajan M, Vasudeva G, Asha K, Rajesh V, Padma G M, Laxminarayana K B. 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 January2010.
4. National AIDS Control organization. Country progress report: UNGASS. India 2010. New Delhi, India;(cited 21September2010).Available at: http://unaids.org/en/knowledgecentre/hivdata/countryprogress/2010CountryProgressAll Countries.asp. Accessed September21,2010. 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 D M, Mohiuddin S, Noorunnisa. Evaluation of incidence of zidovudine induced anemia in Indian human immunodeficiency virus positive patients in comparison with stavudine based highly active antiretroviral therapy. *Int J Risk Saf Med*. 2011;23(3):171–180. https://doi.org/10.3233/jrs-2011-0531
7. Goettler M, Schneewelss S, Hasford J. adverse drug reaction monitoring-cost and benefit consideration part II: cost and preventability of adverse drug reactions leading to hospital admission. *Pharmcoepidemiol Drug Safety*. 1997;6:79–90. https://doi.org/10.1002/(sici)1099-1557(199710)6:3+<s79::aid-pds294>3.0.co;2-o
8. Dukes M N. Economic costs of adverse drug reactions. *Pharmacoeconomics*. 1992;1(3):153–154. https://doi.org/10.2165/00019053-199201030-00001
9. Eisenberg J M. Clinical economics. A guide to the economic analysis of clinical practice. JAMA; 1989;262(20):2879–2886.
10. Senst B L, Achusim L E, Genest R P. 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. https://doi.org/10.1093/ajhp/58.12.1126
11. Hutchinson A B, Farnham P G, Dean H D. 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. https://doi.org/10.1097/01.qai.0000243090.32866.4e
12. Bates D W, Spell N, Cullen D J. The cost of adverse drug events in hospitalized patients. *JAMA*. 1997;277(4):307–311.
13. Simpson K N, Jones W J, 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. https://doi.org/10.2165/00044011-200727120-00002

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://www.aidsinfo.nih.gov/ContentFiles/. *AdultandAdolescentGL.pdf. Accessed January2010*.
15. Study AIDS. Group. Recommendations of National Plan on AIDS: Antiretroviral treatment of HIV-infected adults (January 2008update)[in Spanish].http://www.gesida. Seimc.org. Accessed January2010.
16. Harris M, Montaner J S. Management of HIV-infected patients with multidrug-resistant virus. *Curr HIV/AIDS Rep*. 2004;1:116–121. https://doi.org/10.1007/s11904-004-0017-8
17. Dartneell JGA, Anderson R P, Chohan V. for adverse events related to drug therapy: incidence, availability and costs. *Med J Aust*. 1996;164:659–662.
18. Schneeweiss S, Hasford J, Gottler M, Hoffmann A, Riethling A K, Avorn J. Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study. *Eur J Clin Pharmacal*. 2002;5:285–291. https://doi.org/10.1007/s00228-002-0467-0
19. Bordet R, Gautier S, H Le Louet, J Dupuis B Caron. Analysis of the direct cost of adverse drug reactions in hospitalized patients. *Eur J Clin Pharmacal*. 2001;56:935–841. https://doi.org/10.1007/s002280000260
20. Wasserfallen J B, 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. https://doi.org/10.1016/s0953-6205(01)00159-5
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. https://doi.org/10.1046/j.1365-2125.1998.00667.x
22. Lagnaoul 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.
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. https://doi.org/10.1002/pds.871
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. https://doi.org/10.1002/pds.1907
25. World Health Organization. *Technical Report Series 498.World Health Organization: Geneva*. 1972.
26. Edwards I R, Aronson J K. Adverse drug reactions: definitions, diagnosis and management. *Lancet*. 2000;356:1255–1259. https://doi.org/10.1016/s0140-6736(00)02799-9
27. World Health Organization. *Uppsala Monitoring Center*. Safety monitoring of medicinal products, guidelines for setting 201 up and running phamacovigilance center, Geneva.Available at; 1996. URL: http://www.who.int/en/(accessed25January2011).
28. Hartwig S C, Siegel J, Schneider P J. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm*. 1992;49:2229–32. https://doi.org/10.1093/ajhp/49.9.2229
29. Suh D C, Woodall B S, Shin S K, Hermes D E. Clinical and economic impact of adverse drug reactions in hospitalized patients. *Ann.Pharmacother*. 2000;34:1373–1379. https://doi.org/10.1345/aph.10094
30. Lazarou J, Pomeranz B H, Corey P N. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1998;279(15):1200–1205. https://doi.org/10.1001/jama.279.15.1200
31. Detournay B, Fagnani F, Pouyanne P. Cost of hospitalizations for adverse drug reaction related hospitalizations -cost of to side effects of drugs [Cmlt des hospitalisations pour effet indesirable medicamenteuxl. *Therapy*. 2000;55:137–139.
32. Chen R Y, Accortt N A, Westfall A O. Distribution of health care expenditures for HIV-infected patients. *Clin Infect Dis*. 2006;42:1003–1010. https://doi.org/10.1086/500453
33. Lobas N H, Lepinski P W, Abramowitz P W. Effects of Pharmaceutical care on medication cost and quality of patient care in an ambulatory care clinic. *Am.J.Hos.Pharm*. 1992;49:1681–1688. https://doi.org/10.1093/ajhp/49.7.1681

34. White T J, Arakelian A, Rho J P. Counting the costs of drug-related adverse events. *Pharmacoeconomics*. 1999;15(5):445–458. https://doi.org/10.2165/00019053-199915050-00003
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. https://doi.org/10.1046/j.1365-2125.1998.00667.x
37. Blitz M, Spivack E, Kerpel S, Freedman P. Stevens-Johnson syndrome in an HIV infected patient. *AIDS Read*. 1999;9:184–185.
38. Kumarasamy N, Safren S A, Raminani S R. 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. https://doi.org/10.1089/apc.2005.19.526
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. 2006;26:31–41.
40. Moore R D, Keruly J C, Chaisson R E. Incidence of pancreatitis in HIV-infected patients receiving nucleoside reverse transcriptase inhibitor drugs. *AIDS*. 2001;15:617–20. https://doi.org/10.1097/00002030-200103300-00011
41. Jordi B, Esteban M, Araceli R, Jose L B, Miguel A G, Josep M P, Elisa D L. 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 P F, Maja M, Jan-Nico B B, Luigi N, Cecile V, Jean-CR. Nevirapine and the risk of Stevens –Johnson Syndrome or toxic epidermal necrolysis. *AIDS*. 2001;15:1843–1848.
43. Moore R D. Cost effectiveness of combination HIV therapy: 3 years later. *Pharmacoeconomics*. 2000;17:325–30. https://doi.org/10.2165/00019053-200017040-00002
44. Hellinger F J, Fleishman J A. Estimating the national cost of treating people with HIV disease: patient, payer, and provider data. *J Acquir Immune Defic Syndr*. 2000;24:182–8. https://doi.org/10.1097/00042560-200006010-00016

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