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HAS HAART WON HEART OF HIV/AIDS PATIENTS?

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ABSTRACT

Background: The Human Immunodeficiency Virus (HIV) has changed from life threatening to chronic condition due to the almost universal use and accessibility of antiretroviral treatment (ART) among HIV patients. Antiretroviral (ARV) treatment works by suppressing the viral load and restoring the immune system. Once patients start Highly Active Antiretroviral Therapy (HAART), it is to be continued lifelong in spite of its many adverse side effects. **Objective:** To identify the adverse drug reactions (ADRs) to antiretroviral therapy (ART) and to assess their impact on treatment compliance in patients with HIV/AIDS in western India. **Methods:** A retrospective study was conducted in Gujarat to study the adverse effects after HAART initiation in 1244 patients on HAART who were evaluated retrospectively for their adverse drug reactions (ADRs). **Results:** The most common first line regimen was stavudine+lamivudine+efavirenz (d4T +3TC + EFV)(68.6 %) followed by stavudine + lamivudine + nevirapine (d4T + 3TC + NVP)(17.9%); zidovudine+ lamivudine + nevirapine(AZT+3TC+NVP) (10.9 %); and zidovudine+lamivudine+efavirenz

(AZT + 3TC +EFV) 2.5%. The first line of regimen was modified in 136(10.9%) patients, the most common cause for modifying therapy being development of an adverse effect 721(57.9%) and completion of antituberculous therapy in 510 cases(41.%). The most common cause for modifying therapy was skin rashes due to NVP in 279(22.4%) followed by loss of appetite 195(17.2%). **Conclusion:** A significant proportion of patients had adverse effects of HAART. A significant proportion of those started on NVP-based regimens are more likely to substitute therapy when compared with those on non-NVP-based regimens.

KEYWORDS: HIV, AIDS, ART, HAART, Adverse Drug Reaction (ADR), CD4 Count.

ABBREVIATIONS

HIV – Human Immunodeficiency Virus

AIDS - Acquired immune deficiency syndrome

ART - Antiretroviral Treatment

ARV – Antiretroviral

HAART - Highly Active Antiretroviral Therapy

ADR - Adverse Drug Reaction

INTRODUCTION

The Human Immunodeficiency Virus (HIV) has changed from life threatening to chronic condition due to the almost universal use and accessibility of antiretroviral treatment (ART) among HIV patients [1]. Antiretroviral (ARV) treatment works by providing suppression of viral load and restoring the immune system. It is estimated that out of the 35.3 million people living with HIV worldwide, 10.6 million were receiving ART in 2012 [2]. Nearly, 6.6 million HIV/AIDS related deaths worldwide have been prevented as a result of ART [2]. Despite these gains, adverse reactions to these medicines remain a significant public health concern and may compromise the effectiveness of the ART programmes [3,4].

In India, approximately 2.4 million people were living with human immunodeficiency virus (HIV) in 2009, which is estimated to be the third largest population of HIV affected people in the world.[5] With the availability of new antiretroviral drugs, there has been a decline in morbidity and mortality due to acquired immunodeficiency syndrome (AIDS).

The advent of highly active antiretroviral therapy (HAART) has resulted in significant decreases in HIV-related morbidity and mortality in both the developed and developing

world[6-8] and HAART has been touted as one of the greatest breakthroughs in the response to the HIV pandemic. HAART may be modified or interrupted as a result of many reasons, key among which are adverse effects and virological failure [8-11]. The adverse effects may in themselves result in virological failure or disease progression as a result of sub optimal dosing or treatment interruption.

In a study done in India, 90.6% of all the patients on HAART developed an adverse drug reaction and there were 618 episodes in various systems, the abdominal and central nervous systems were the most affected [12]. Luma and colleagues, studying patients in Cameroun found an adverse drug reaction (ADR) prevalence of 19.5% of which 21.2% were due to peripheral neuropathy. Overall 56.1% of ADR were attributed to the use of stavudine (d4T)[13]. Anaemia was observed as an ADR in many patients on ART, especially whenever the patients took zidovudine (ZDV) [14].

In an effort to scale up HAART to those who needed it most, the WHO in 2003 launched the "3 by 5" initiative with an objective of placing 3 million persons living with HIV on HAART by 2005[15]. In line with this initiative the World Health Organisation (WHO) developed guidelines on antiretroviral therapy for resource poor countries. The guidelines recommended a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) as first-line regimens in resource-constrained settings[16].

Access to antiretroviral therapy (ART) has improved tremendously over the last few years due to implementation and enforcement of various strategies by National AIDS Control Organization (NACO). NACO has established ART centres in selected government hospitals which offer free treatment for HIV/AIDS and related opportunistic infections. [17] In India, as of May 2009, there were 174 ART centres and 1,55,000 patients were on therapy. [18] By 2012, National AIDS Control Program III (2007-2012) aims to increase number of ART centres up to 250 where 3,00,000 adults will be given free ART. [17] In addition, 10 centres of excellence responsible for training, research work and mentoring of ART centres linked to them have been established across the country.[19]

HAART is the corner stone of management of patients with HIV/AIDS infection. [20] Consistent use is vital for drugs to be effective and to prevent emergence of resistance. However, ARV drugs are highly toxic and are associated with various adverse

drug reactions (ADRs) due to which many patients require withdrawal of the drug or even discontinue the treatment resulting in treatment failure. [21] Hence, monitoring and reporting of ADRs in HIV/AIDS patients receiving ART assumes great importance. There is paucity of data on ADRs to ART in Indian population. Keeping this in view, the present study was designed to identify the ADRs in patients receiving ART and to assess their impact on the compliance to the prescribed treatment.

MATERIAL AND METHODS

It was a retrospective study conducted at various ART centres of western India. The study was approved by GSACS, Ahmedabad.

A cross sectional retrospective study was conducted reviewing data of 1244 patients initiated on HAART. Univariate analysis was done for the dependent and independent variables. Stepwise logistic regression procedures were used to model the effect of gender on the development of ADRs controlling other variables like age, marital status, weight at baseline and CD4 at baseline.

From the patients records, findings of complete general, physical, systemic examination and all laboratory investigations were recorded. ADR monitoring was done in a systemic manner adopting both spontaneous and intensive monitoring approaches. The WHO definition of an ADR was adopted [22]. A pre-designed and pre-tested proforma had been confidentially used for ADR record keeping.

If the patient developed any ADR, the drug which was most commonly implicated in the causation was challenged by the treating physician and was replaced by another drug from the same class. The patient was then monitored for recovery from the symptoms.

The World Health Organisation (WHO) ADR probability scale was used for causality assessment.

With respect to ADR, following parameters were recorded.

1. Number of adverse drug reactions with different treatment regimens,
2. Nature of adverse drug reactions,
3. Severity of adverse drug reactions,

4. Incidence of each adverse drug reaction-calculated by dividing the number of patients suffereing from a particular adverse drug reaction by the total number of patients taking the same suspected drug,
5. Requirement of de-challenge,
6. Compliance to the prescribed treatment- monitored by pill count at each visit and as reported by the patient, and
7. Number of deaths.

RESULTS AND DISCUSSION

One thousand two hundred forty four (1244) patients who had been on ART were included in the present study, Out of which 1132(90.99%) patients complained of ADRs and few of them even recorded to have multiple ADRs.

Patients received four first line regimens as per the NACO guidelines [Table 1]. Stavudine +Lamivudine + Efavirenz was the most widely used combination [Table 2]. Drugs were given in the following dosages: Stavudine 40 mg B.D., Lamivudine 150 mg B.D., Nevirapine 150 mg B.D., Zidovudine 300 mg B.D. and Efavirenz 600mg H.S.

Out of the 1244 patients enrolled, 1132(90.99%) patients were recorded to report ADRs. About 74.91 % were recorded to develop more than one adverse reaction. A total of 1511 adverse drug reactions affecting various systems were observed in 1132 patients [Table 3]. Majority of adverse reactions were observed related to the gastrointestinal system and central nervous system including loss of appetite and insomnia each accounting for 28 percent. Maximum adverse reactions (872 out of 1511) were observed in patients who were prescribed treatment Ia (Stavudine + Lamivudine + Nevirapine). This was followed by 338 ADRs in patients receiving treatment regimen IIa, 223 ADRs in the patients taking treatment regimen I, and 78 ADRs in the patients taking treatment regimen II.

Irregular menstrual cycle was reported by 10 patients, 3 each in treatment I, II, and IIa. Loss of smell sensation and hearing impairment was observed in 2 patients receiving treatment regimen I and in 3 patients in regimen Ia.

Incidence of ADRs to a particular drug was calculated based on only the dechallenge test. Incidence of peripheral neuropathy and fat redistribution due to stavudine was 6.98% and

2.67%, respectively, and incidence of skin rash due to nevirapine was 7.23%, incidence of hepatitis due to nevirapine and efavirenz was 2.96% and 2.17 % respectively.

Even though HAART showed plenty of adverse drug reactions, at the same time it decreased morbidity and mortality in HIV/AIDS patients, it improved health status, body weight and even CD4 counts in almost about 90 % of the patients who adhere to this treatment strictly [Table 4].

The basic configuration of antiretroviral regimens is unchanged. The most common initial regimens are a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) with two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). Common toxicities of ART can make adherence to therapy difficult. However, adherence is important to prevent the development of drug resistance. Unlike therapy for other diseases, a strategy of decreasing the dose or switching to a different drug to minimize toxicity and maximize adherence may not be possible with ART; the benefit of suppressing HIV may override other considerations. Identification and awareness of ART toxicity are necessary to facilitate patient adherence and determine when a change in therapy may be needed.

Routine monitoring in patients receiving ART includes a complete blood count and a comprehensive metabolic panel every three to six months. A lipid profile and urinalysis for proteinuria should be performed annually. When ART is changed, a complete blood count, metabolic panel, and lipid profile should be performed two to eight weeks afterward. Abnormal results should prompt more frequent testing based on clinical assessment.

According to Joint United Nations Programme on HIV and AIDS (UNAIDS) and WHO estimates, approximately 1,58,000 people all over the world were receiving ART in 2007[23]. It is well known that anti-retroviral drugs are highly toxic and therefore, early detection of ADRs by continuous monitoring is indispensable for successful treatment. In the present study, 1511 ADRs were observed in 1132 (90.99%) patients. Main risk factors associated with development of ADRs in HIV patients as determined by the researchers in previous studies included illiteracy, female gender, CD4 < 200 cells/µL, and opportunistic infections such as tuberculosis.[24] Earlier studies have also documented that a majority of ADRs were predictable and preventable.[24,25]

We observed that the maximum numbers of ADRs were related to the gastrointestinal system which is in agreement with findings of Modayil *et al*.[24] In our study, apparently maximum ADRs occurred in patients receiving stavudine+lamivudine+efavirenz which may be attributable to larger number of patients receiving this combination; however, it was observed that the incidence of ADRs was highest with the stavudine+lamivudine+nevirapine regimen.

Most cases (18/21) of peripheral neuropathy and all cases of lipodystrophy were observed in patients receiving stavudine therapy. Similar findings have been reported earlier. [24] We observed an incidence of 1.39% of peripheral neuropathy but no case of fat redistribution with stavudine. However, earlier studies have reported an incidence of peripheral neuropathy as 10%, 12% and a prevalence of lipodystrophy as 25%.[26,27.28] Low incidence seen in our study may be contributed to under diagnosis and that the drug is well tolerated in this part of the world. Recently updated WHO guidelines on ART for HIV/AIDS patients do not recommend use of stavudine as a first choice in first-line regimens due to these adverse effects.[20]

Incidence of skin rash (18.46%) and hepatotoxicity (3.19%) due to nevirapine seen in our study was almost the same when compared to that observed by Rotunda *et al*. (skin rash-15%),[29] Martinez *et al*. (hepatotoxicity-12.5%),[30] and Sulkowski *et al*. (hepatotoxicity-15.6%).[31] Latter also reported that the incidence of hepatitis due to efavirenz was 8%, whereas we found an incidence of only 0.43%. Further, in our study dechallenge with nevirapine and efavirenz in these patients resulted in resolution of hepatitis gradually over a period of 3 weeks and 1 month, respectively.

Few ADRs never documented earlier in the literature with use of ART such as irregular menstrual cycle, hearing impairment and loss of smell were also observed in the present study.

Issue of non-compliance is of major concern in management of HIV patients keeping in view that it requires lifelong treatment. Non-compliance causes significant economic implications by complicating disease management and its subsequent healthcare and social costs. Earlier studies have documented that most important factor resulting in non adherence to ART is toxicity.[32] We observed that it was mainly the severe ADRs which affected the patients' compliance. We observed that 22.1% of patients were non-compliant to ART because of

ADRs. These findings are in concordance with that of Monforte *et al.* who reported non compliance in 21.1% of Italian patients due to ADRs to ART.[32]

The risk of adverse drug reactions (ADRs) arises because of the effect of the disease on the immune systems and the safety profiles of the complex ART drugs [3]. There are a number of ADRs related to ART that have been documented, and may be mild to severe; and short to long term depending on the environment[1,5,33]. ADRs in developing countries may differ from those in developed countries because of high prevalence of conditions such as malnutrition, tuberculosis and patients presenting with advanced HIV disease [34]. For instance, it has been found that in Africa, neuropathy, neutropenia and lipodystrophy are the predominant ADRs[35]. Short term ADRs are a potential threat to successful initiation and adherence to ART[36]. The timing of ADRs may also depend on the type of drugs. Studies have shown that patients on Efavirenz, Lamivudine and Zidivudine or Indinavir, Zidovudine and Lamivudine may present with ADRs within the first 12 and 24 weeks, respectively[37]. ADRs may be common or specific to class of drugs [1,36]. Drugs classified as non-nucleoside reverse transcriptase inhibitors (NNRTIs) which include Efavirenz (EFZ) and Nevirapine (NVP) are known to cause rashes and hepatotoxicity. On the other hand, drugs classified as nucleoside reverse transcriptase inhibitors (NRTIs) including Zidovudine (AZT) and Stavudine (d4T) are known to cause anaemia, nausea, rashes, lipoatrophy and lactic acidosis.[1]

Apart from ADR depending on the environment and the type of ART regimen, a number of other risk factors have been identified, that include patient age, gender, duration of treatment, disease biomarkers such as CD4 count and viral load and body mass index (BMI) [38]. These risk factors have been found to interact with type of ADR. For instance, females are more likely to develop rashes and hepatotoxicity[38]; and patients aged 40 years and above are at a higher risk of developing peripheral neuropathy when taking d4T[39]. The longer a patient is on ART the less likely they would experience ADRs; possibly as a result of stability in ARV regimen, coming after many changes and eventually settling on an acceptable regimen [30].

Monitoring safety and toxicity related to ART remains a challenge facing the public health sector. Monitoring is usually done using spontaneous surveillance of HIV patients on treatment. Spontaneous reporting of ADRs is a very inefficient system in detecting drug-related conditions, leading to underestimation of the burden due to ADRs [3,40]. Thus, more systematic and robust surveillance methods including structured surveillance

pharmacovigilance systems, which assess and monitor safety profile and impact of antiretroviral medicines have been advocated. Structured surveillance tracks HIV positive patients who are on ART to assess drug related morbidity and mortality over time. South Africa, a country heavily hit by the HIV epidemic, uses spontaneous surveillance of HIV patients on ART to assess ART-related adverse effects. Though these data are routinely available, the coverage may not be adequate. Thus, for the purposes of this study, data from a structured surveillance system in Western India are used.

The adverse drug reaction events in patients often are of recurrent nature, such that the repetitions tend to cluster more in some patients than in others. Analyses of these data are complicated due to the fact that independence between the recurrent event times cannot be predicted in a subject. In medical studies, time-to-event models have been developed to account for possible dependence between recurrent events data [42]. The aim of this study was to provide a unified analysis of recurrent ADR events data from a structured antiretroviral pharmacovigilance surveillance system.

Table 1: Treatment Regimens as per NACO guidelines.

Treatment Regimens	Drugs in combination	No Patients
I	Zidovudine + Lamivudine + Nevirapine	136
Ia	Stavudine + Lamivudine + Nevirapine	223
II	Zidovudine + Lamivudine + Efavirenz	31
IIa	Stavudine + Lamivudine + Efavirenz	854

Table 2: Patient's characteristic in different treatment groups.

	Treatment regimen I	Treatment regimen Ia	Treatment regimen II	Treatment regimen IIa
No of patients	136	223	31	854
Mean Age(years)	36 + 8.34	40 + 2.87	33 + 7.20	38 + 4.31
Sex(M/F)	92/44	155/68	20/11	532/322
Weight (kg)	50 + 6.65	53 + 9.22	51 + 5.13	58 + 5.22
Current CD4 count				
< 200	43	78	21	247
> 200	93	145	10	607

Table 3: ADRs related to different systems.

System Involved	No. of patients with ADRs (%)
Gastrointestinal system	**678(36.45%)**
Loss of appetite	195(28.76%)
Dyspepsia	154(22.71%)
Abdominal Discomfort	81(11.94%)

Diarrhoea	74(10.91%)
Constipation	54(07.96%)
Nausea	51(07.52%)
Vomiting	43(06.34%)
Abdominal Pain	21(03.10%)
Hepatitis	05(00.59%)
Central Nervous System	**415(22.31%)**
Insomnia	111(28.75%)
Headache	89(21.45%)
Dizziness	78(18.80%)
Anxiety	57(13.73%)
Nightmare	27(06.51%)
Peripheral neuropathy	21(05.06%)
Excessive sleep at night	19(04.58%)
Delusion	14(03.37%)
Dermatological	**287(15.43%)**
Skin rashes & itching	279(97.21%)
Facial discolouration	08(02.79%)
Metabolic	**178(09.57%)**
Fatigue	109(61.24%)
Dyspnea	69(38.76%)
Musculoskeleton	**106(05.70%)**
Body ache	51(48.11%)
Vague chest pain	28(26.41%)
Pain in legs	27(25.47%)
Miscellaneous	**15(00.81%)**
Irregular menstruation	10(66.67%)
Loss of smell sensation	3(20.00%)
Hearing impairment	2(13.33%)

Table 4: Descriptive analysis of socio-demographic and health status of the patients at ART clinic.

	Variables	**n(%), N = 1244**
1	**Socio-demographic**	
(i)	Education (primary and above)	871(70.1)
(ii)	Work status (unemployed)	247 (19.9)
(iii)	Age (≤40 years)	705(56.7)
(iv)	Gender (female)	445(35.8)
(v)	Marital status (married)	1068 (85.9)
(vi)	Residency (urban)	466 (37.5)
2	**Clinical variables**	
(i)	Duration of ART (≤4 years)	495(39.8)
(ii)	Current CD4 level (cells/mm^3)	
a.	< 200	389(31.3)
b.	>200	855(68.7)
(iii)	Non adherence	47(3.8)
3	**General profile**	
	General health at the start of treatment	

(i)	Healthy	257(20.67)
(ii)	Mild to severely ill	987 (79.5)
4	**CD $_4$ count after treatment**	
(i)	Increased	1135 (91.2)
(ii)	Decreased	27(2.1)
(iii)`	No change	82(6.6)
5	**Health status after ART start**	
(i)	Improved	1114(89.5)
(ii)	Not improved	130(10.4)
6	**Body weight**	
(i)	Increased	1009(84.1)
(ii)	Decreased	91(7.3)
(iii)	No change	144(11.6)

CONCLUSION

HAART has decreased morbidity and mortality up to the expectation along with increasing considerable longevity of life of the HIV/AIDS patients. But all these antiretroviral drugs are highly toxic and associated with myriad adverse drug reactions and that too with a very high frequency. These ADRs are adding to the problem of non-compliance which in itself is a very big issue with ART. Hence, it is prudent to recognize these ADRs as early as possible in the course of treatment. This goal can be achieved by regular monitoring and reporting of ADRs which is indispensable for improving the treatment outcome.

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