



## Highly Active Antiretroviral Therapy: Incidence of Adverse Drug Reactions

Languluri Reddenna\*, Shaik Ayub Basha, Donthu Venu Gopal, Tedlla Rama Krishna  
Pharm-D Intern, Department of Pharmacy Practice, P.Rami Reddy Memorial college of  
Pharmacy, Utukur, Kadapa, Andhra Pradesh, India-516003.

### ABSTRACT

The Acquired Immunodeficiency Syndrome (AIDS) was first recognized in 1981, in the United States of America in young homosexual men who had Kaposi sarcoma and serious infections. HIV is transmitted through unprotected sexual intercourse, transfusion of contaminated blood, sharing of contaminated needles and between a mother and her infant during pregnancy, childbirth and breastfeeding. In India, an estimated 0.1 percent of adults aged 15-49 are living with HIV, which seems low when compared to HIV prevalence in some parts of sub-Saharan Africa. The HIV prevalence at antenatal clinics was 1% in 2007. This number is smaller than the reported 1.26% in 2006, but remains the highest out of all states. HIV prevalence at STD clinics was very high at 17% in 2007. Although adverse reactions are common and often predictable, their management must be individualized. In addition, the patient's report of severity can be inconsistent with the clinical interpretation and this must be considered when determining the management of adverse reactions. Antiretroviral therapy is effective for HIV treatment but also increasingly complex. The many adverse effects of therapy may cause symptoms affecting a variety of organ systems. Patient non adherence is the reason for the treatment failure for antiretroviral therapy. To optimize adherence treating physicians must focus on early detection and prevention of ADRs, when possible and distinguishing those that are self-limited from those that are potentially serious. The pharmacist should be able to detect ADRs and the culture of reporting ADRs should be instructed. All ART centers should have Pharmacovigilance cell. All ADRs reported should be analyzed as per WHO guidelines on causal assessment. Our study concluded that there is a need of the active Pharmacovigilance Centre with intensive monitoring for ADRs by the Pharmacist in Indian HIV positive patients.

**Key words:** ADRs, AIDS, ART, HIV, HAART

### INTRODUCTION

India is one of the most populated countries in the world, with over one billion inhabitants. Of this number, it was estimated that around 2.4 million people are currently living with HIV.<sup>[1]</sup> HIV was probably a mutation of an African monkey virus. The presence of related retroviruses in African monkeys and apes and the close relationship of HIV to Chimpanzee. The Acquired Immunodeficiency Syndrome (AIDS) was first recognized in 1981, in the United States of

Kaposi sarcoma and serious infections. HIV is transmitted through unprotected sexual intercourse (anal or vaginal), transfusion of contaminated blood, sharing of contaminated needles, and between a mother and her infant during pregnancy, childbirth and breastfeeding.<sup>[2]</sup> Treatment options for HIV infected people were very limited, which has been demonstrated to affect the behavior of the virus itself, were not available.<sup>[3]</sup>

By the early 1990s, AIDS epidemics had emerged in several Asian countries and by the end of the decade; HIV was spreading rapidly in many areas

of the continent. At present, around 4.87 million people are living with HIV in South, East and South-east Asia. Even though, national HIV prevalence in most Asian countries is relatively low, the population of some countries is consequently vast that these low percentages actually represent very large numbers of people living with HIV. In India, an estimated 0.1 percent of adults aged 15-49 are living with HIV, which seems low when compared to HIV prevalence in some parts of sub-Saharan Africa. Andhra Pradesh has a total population of around 76 million, of whom 6 million live in or around the city of Hyderabad. The HIV prevalence at antenatal clinics was 1% in 2007. This number is smaller than the reported 1.26% in 2006, but remains the highest out of all states. HIV prevalence at STD clinics was very high at 17% in 2007. Among high-risk groups, HIV prevalence was highest among men who have sex with men (MSM) (17%), followed by female sex workers (9.7%) and injection drug users (IDUs) (3.7%).<sup>[4]</sup>

Antiretroviral therapy (ART) is treatment for human immunodeficiency virus (HIV) using anti-HIV drugs. The standard treatment consists of combination of at least three drugs (often-called highly active antiretroviral therapy or HAART) that suppress HIV replication. The introduction of the highly active antiretroviral therapy (HAART) has led to significant reduction in AIDS-related mortality and morbidity. The advent of antiretroviral drugs in early 1990's began a revolution in the management of HIV infection. Three groups of ARV drugs had successful in interrupting the viral replication. Strict adherence, the use of combination of three drugs leads to sustained viral suppression for several years. However, antiretroviral therapy (ART) does not cure HIV/AIDS, but effective antiretroviral regimens inhibit the efficient replication of the HIV virus, and reduce viremia to undetectable levels.

The first drug effective against HIV, Zidovudine (AZT, ZDV) was approved as early as 1986. Until early nineties, only Zidovudine (ZDV) & Didanosine were available and used as monotherapy. By the year 1995, results from several studies had demonstrated that use of two-nucleoside analogue combined (dual therapy) was quite effective in delaying the disease progression, showed an impressive clinical improvements and increase in CD4 counts. The situation changed dramatically in 1996 with the introduction of Protease Inhibitors (PIs), which were very potent drugs and reduced the viral load by 10 – 100

times. Because of effective triple combination therapy, hospitalization rates of HIV infected individuals reduced dramatically. The drugs were no doubt quite efficacious but were associated with problems of significant toxicities, adherence to large number of pills (20 – 30 per day) and high costs.

Currently, we had 21 anti-retroviral agents approved by US FDA, of which 15 currently available in India. The efficacy of drugs was well documented, options available are several and large numbers of patients are on ARV therapy. Yet, the management of HIV is becoming increasingly complex as problems of long-term toxicities; drug-drug interaction and drug resistance are emerging. There are matters about wide availability of monitoring facilities like viral load, drug resistance testing, and second line ARV drugs.<sup>[5]</sup>

### **Goals of Anti retroviral therapy**

The primary goals of antiretroviral therapy were maximal and durable reduction in plasma viral levels, restoration of immunological functions aimed at prolongation of life and improvement in quality of life.<sup>[6]</sup>

### **Principles of Anti retroviral therapy**

A continuous high level of replication of HIV takes place in the body right from the early stages of infection. The HIV destroys CD4 Cells, while body produces more CD4 cells. This balance is maintained for some years after which the rate of CD4 destruction becomes more than that of CD4 production. This progressive immune system damage results in susceptibility to different opportunistic infections (OI), malignancies, neurological diseases, wasting and, ultimately, death. A combination of at least three agents from different classes of ARV drugs is the regimen of choice and gives maximal achievable suppression of HIV replication over a prolonged period. Regular measurements of CD4 cell count and plasma HIV RNA levels (if possible) are necessary to determine the risk of disease progression in HIV infected patients and to determine when to initiate or modify ART regimens. The viral load levels indicate the magnitude of HIV replication while CD4 counts indicate the extent of HIV induced immune damage. The antiretroviral drugs act on various stages of replication of HIV in the body and interrupt the process of viral replication. Commonly used agents, target the virus mainly by inhibiting the enzymes reverse transcriptase (RT Inhibitors), and protease (Protease Inhibitors). The

newer group of drugs includes Fusion Inhibitors, integrase inhibitors, CCR5 antagonist and second generation NRTIs.

### **ART Initiative in India**

There is an estimation of 2.31 million people living with HIV/AIDS in India. As per estimates, at any given time approximately 10-15% of the total numbers of people with HIV infection are expected to be in need of ART. This means nearly 3-4 lakh patients will need ART presently. Until now, the high costs and complicated treatment regimens were the major barriers in introducing free ART. With advent of newer ARV drugs with lesser side effects and lowered costs, it was considered appropriate to introduce provisioning free ART through public sector health facilities in a phased manner.<sup>[7]</sup>

ART had initiated and when the patient becomes eligible according to the technical guidelines. However, before starting the ART, it is of utmost importance to ensure that the patient was well prepared for the therapy. The preparedness includes that the patients has adequate understanding of the disease, should aware of the treatment regimens, importance of adherence to therapy, and is willing to take the treatment. The adequate preparedness of the patient is critical in ensuring a high level of adherence to ART. It is also important to have reliable laboratory services for investigations such as complete blood count and biochemistry, access to CD4 count and viral load facilities are needed. One has to ensure reliable, affordable and uninterrupted access to quality antiretroviral drugs, and drugs to treat opportunistic infections and other related illness.

Prior to starting therapy, it is essential to undergo a clinical evaluation, so as to assess the present stage of HIV infection, presence of any Opportunistic Infection (Present or Past) and identifying co-existing medical conditions. The patient should have a detailed physical examination and should undergo investigations like complete blood count, chest X-Ray, renal and liver function, lipid levels, VDRL, Hepatitis B & C serology, pregnancy testing and urine for routine and microscopic examination and CD4 counts.<sup>[8]</sup>

### **Adverse drug reactions with HAART therapy**

Any drug may produce unwanted or unexpected adverse reaction. Detection, recording and reporting of these reactions is of vital importance. Doctors, pharmacists and nurses have the

responsibility to participate in this programme. Adverse reactions are significant cause of morbidity, mortality and can affect adherence to treatment schedule and increase risk of resistance and relapse of disease. ARV drugs have lower safety profile and given the facts that they need to be taken on chronic basis, patients who are immunodeficient consume them and immunodeficient patients are more prone to develop adverse reaction to any drug. Hence, it is important that patients receiving ARV drugs or other drugs closely monitored for ADRs and they are managed appropriately so that adherence to the prescribed treatment is ensured.<sup>[9]</sup>

A study conducted by Radhakrishnan rajesh et al,<sup>[10]</sup> found that anemia and hepatotoxicity were the most commonly observed ADRs. The organ system commonly affected by ADR was red blood cell (21.4%). The ADRs were moderate in 77% of cases. Type A reactions (77%) were more common. 10.8% ADRs were definitely preventable. The incidence rate of ADRs (65.9%) was highest with Zidovudine + Lamivudine + Nevirapine combination. 84% interruptions to highly active antiretroviral therapy were due to toxicity. CD4 less than 200 cells/ $\mu$ l, female gender and tuberculosis were observed as risk factors for ADRs. They concluded that incidence of ADRs in intensively monitored patients was found to be 43.8%. Anemia in HIV patients is an influential risk factor for occurrence of ADRs. With the increasing access to antiretroviral in India, clinicians must focus on early detection and prevention of ADRs to highly active antiretroviral therapy. Another study conducted by Hossein Khalili et al,<sup>[11]</sup> found that 87.6% of patients showed at least one ADR. Prevalence of ADRs based on affected organ was gastrointestinal (GI) (63.7%), hematological (32.6%), neurological (30%), cutaneous (22%), musculoskeletal (21.3%), hepatic (20%), metabolic (18.6%), and renal (2.6%) adverse effects. The most important results of this study was finding of hematological ADRs as the most common cause of ART interruption, supporting the hypersensitivity nature of antiretroviral induced hepatotoxicity especially cholestasis and new finding of the significant positive correlation between hepatitis C virus co-infection and the occurrence of ART induced skin reactions. DR. Marfatia Y.S. et al,<sup>[12]</sup> review on adverse drug reactions (ADR) due to Antiretrovirals (ARV): Issues and challenges. In a review of over 1000 patients in a Swiss cohort that received combination ARV therapy, 47% and 27%

of the patients were reported to have clinical and laboratory adverse events, respectively. Cutaneous manifestations of ADR can serve as surrogate marker of internal involvement. Dermatovenereologists can play a crucial role in identifying and managing ADR.

Michelle M Foisy et al<sup>[13]</sup> conducted a study hospitalization due to adverse drug reactions and drug interactions before and after HAART. To characterize and compare the rates of adverse drug reactions (ADRs) and interactions on admission in two, one-year periods: pre-highly active antiretroviral therapy (HAART) (phase 1) and post-HAART (phase 2). In phase 1, 436 of 517 admissions, and, in phase 2, 323 of 350 admissions were analyzed. Over 92% of patients were male, with a mean age of 38 years. Significant differences ( $P < 0.05$ ) in the mean length of stay (12.08 versus 10.02 days), the CD4 counts (99.25 versus 129.45) and the number of concurrent diseases (4.20 versus 3.63) were found between phase 1 and 2, respectively. The mean number of medications taken (5.52 versus 5.94) and the rates of hospitalization with ADRs (20.4% versus 21.4%) or interactions (2.5% versus 2.16%) were similar between the two phases. Antiretrovirals were more common in ADR admissions post-HAART (21.3% versus 36.2%), while antiparasitics, psychotherapeutics and antineoplastics were more common pre-HAART. Other classes of drugs involved in both phases were sulphonamides, narcotics, ganciclovir, foscarnet, antimycobacterials and antifungals. ADR causality was possible or probable in more than 80% of cases. Over 60% of ADRs were grades 3 to 4, and about 85% were either the main or contributing reason for admission. About 65% of patients had at least partial recovery at the time of discharge. In phases 1 and 2, 8.9% and 2.9% of admissions, respectively, with ADRs were fatal.

Michael Carter et al,<sup>[14]</sup> found that HAART patients at greater risk of severe side effects. The investigators wished to establish the incidence and determinants of serious or life-threatening treatment side effects, AIDS-defining illnesses and death. Data was analyzed from 2,947 patients who were followed for a median of 20.7 months, contributing 5,940 person-years of follow-up. The cumulative percentage of patients with a severe or life threatening side effect at month twelve was 15.6%, at month 24, 23.7% and at month 36, 30.8%. The corresponding percentages for AIDS events were 7.3%, 10.8%, 16.5%, and the

percentages for deaths were 3.9%, 7.9% and 13.1%. When the investigators looked at the risk factors for the experience of severe or life-threatening side-effects, they found that the risk was lower in younger patients (hazard ratio [HR] 0.83 for every decade in years,  $p = 0.0001$ ), and patients who had never taken anti-HIV drugs before (HR=0.59,  $p = 0.0001$ ). The risks were increased for individuals with a history of injecting drug use (HR=1.41,  $p = 0.0006$ ), lower baseline CD4 cell count (for every 100 cells/mm<sup>3</sup>, HR=1.06,  $p = 0.04$ ), and a prior AIDS-defining illness (HR=1.22,  $p = 0.03$ ).

Harminder Singh et al,<sup>[15]</sup> found that 79 HIV positive patients were analyzed. Among them, 68 (86%) had at least one ADR. The most common ADR in our study was peripheral neuropathy (20.83%), followed by skin rashes (15.83%). Female patients had more ADRs (45.71%), than Males (11.36%). Thus management requires a highly precise balance between benefits of durable HIV suppression and the risks of drug toxicity to achieve the therapeutic goals, with conventional drug or with newer less toxic agents.

Valentina Montessori et al,<sup>[16]</sup> found that the suppression of plasma viral loads to less than the limit of quantification of the most sensitive commercially available assays (i.e., less than 50 copies/mL) and the coincident improvement in CD4 T cell counts is associated with resolution of established opportunistic infections and a decrease in the risk of new opportunistic infections. However, prolonged treatment with combination regimens can be difficult to sustain because of problems with adherence and toxic effects. All antiretroviral drugs can have both short-term and long-term adverse events. The risk of specific side effects varies from drug to drug, from drug class to drug class, and from patient to patient. A better understanding of the adverse effects of antiretroviral agents is of interest not only for HIV specialists as they try to optimize therapy, but also for other physicians who care for HIV positive patients.

Le Beller C et al,<sup>[17]</sup> found that distribution of ADRs were metabolic (26%), digestive (22%), psychiatric (13.5%) and cutaneous (12.5%) disorders. Specified in 37 cases, the level of discomfort induced by ADRs was important, very important or unbearable in 70% of cases. According to PV criteria of seriousness, only five cases (12%) were recorded as serious. All ADRs reported by patients were well known and no new

signal on HAART safety was detected. However, this study has given information about the feeling of HIV patient experiencing ADRs under HAART, which could lead to discontinue therapy. The two ADRs reporting systems might be complementary. A significant difference was outlined between patient opinion and PV criteria for ADRs seriousness compared to patient discomfort and causal relationship between ADRs and HAART.

O.M.S. Minzi et al,<sup>[18]</sup> found that anaemia, liver toxicity, skin rash and peripheral neuropathy were the most reported ADRs. The NVP plasma level determination revealed that there was no difference between those who had experienced skin rashes and those who did not (mean of 6.05 and 5.5µg/ml respectively). There was a slight increase in reported ADRs between 2005 and 2006.

Adverse effects had reported with all antiretroviral drugs and are among the most common reason for switching or discontinuing therapy as well as medication non-adherence. The incidence of ADRs with newer antiretroviral regimens is generally declining now (less than 10%). Several factors may predispose individuals to certain antiretroviral associated ADRs viz., women seem to have higher propensity of developing "Steven-Johnson Syndrome" and "Symptomatic drug Hepatic" events with nevirapine and high rate of lactic acidosis with NRTIS. Other factors include concomitant use of medication, co-morbid condition co-infections, - drug interactions or generic predisposition viz., abacour hypersensitivity reaction.

Although therapeutic goals of antiretroviral therapy include achieving, maintaining viral suppression and improving patient immune function, an overarching goal should be to select a regiment that is not only effective but is also safe. This requires taking into account an individual patient's

underlying conditions, concomitant medication and history of drug intolerance.<sup>[19]</sup>

Clinicians and patients face many challenges associated with antiretroviral (ARV) therapy. These include decisions about when to start therapy, what regimen to start with, when to change medications, and how to switch if a regimen is failing. Although clinical research should guide the selection of ARV regimens, it is important to remember that the best regimen for any individual patient is the regimen he or she is willing and able to take. No regimen, no matter how potent, will be effective if the patient does not take it properly. Adherence to ARV therapy is one of the most important predictors of treatment efficacy. Although many factors may interfere with adherence to ARV therapy, adverse reactions to the medications are among the most important. In one trial, patients with adverse events were 13 times less likely than those without adverse events to have 95-100% adherence. Monitoring and managing adverse reactions to ARVs are crucial to establishing a successful HIV regimen.<sup>[20, 21]</sup>

## CONCLUSION

Although adverse reactions are common and often predictable, their management must be individualized. Several factors will affect the management of adverse reactions, including comorbid conditions; the patient's other current medications, the availability of alternative regimens, and the patient's history of medication intolerance. In addition, the patient's report of severity can be inconsistent with the clinical interpretation (i.e., some patients may overemphasize symptoms, whereas others under emphasize symptoms), and this must be considered when determining the management of adverse reactions.

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