

# A study to assess adverse drug reactions to anti retro viral therapy

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## Abstract

**Introduction:** Acquired immune deficiency syndrome is a chronic and potentially fatal disease of the immune system caused by the Human immunodeficiency virus. Highly active antiretroviral therapy (HAART), a combination of at least three drugs for HIV-1 infection has led to substantial reductions in morbidity and mortality. Adverse effects have been reported with all ARV drugs and are among the most common cause for switching or discontinuing therapy as well as medication non adherence. Hence evaluation of ADRs may help clinicians to optimize the drug regimens. Based on these objectives of this study is to assess risk factors related to antiretroviral therapy induced ADR and to assess causality and Severity assessment of reported ADRs.

**Material and methodology:** A prospective study was conducted in HIV positive patients attending ART centre at Government Dharmapuri Medical college, Dharmapuri. Totally 150 patients were included in the first 6 months after initiation of the study and followed up over a period of next 6 months. At follow up visit's patients underwent detailed clinical evaluation with special emphasis on any new symptoms. Causality assessment of ADRs was done by Naranjo algorithm and Severity assessment of ADRs by Hartwig and Seigel's severity scale.

**Results:** In our study out of the 150 patients 56 (37.3%) had experienced ADRs. Majority of ADRs occurred in patients aged 14-50 years (85.7%). Majority of adverse drug reactions occurred in first 2 weeks of antiretroviral therapy. Most of ADRs were related to Hematological (32.1%), Gastrointestinal system (26.8%) and CNS (21.4%). Most of the ADRs were with Zidovudine + Lamivudine + Nevirapine regimen (73.2%). Naranjo causality assessment showed 60% were possible, 32.5% were probable and 7.5% definitive ADRs. Of the total adverse drug reactions 48.2% were mild and 51.8% were moderately severe in intensity.

**Conclusions:** ADRs among the patients with ART regimen is a critical public health issue for Anti- retroviral treatment adherence. Therefore, continuous monitoring is required to prevent severe ADRs and to improve patient compliance.

**Keywords:** Adverse drug reactions; Antiretroviral therapy; Human Immunodeficiency Virus.

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## 1. Introduction

Human immune deficiency virus (HIV) infection and its progression to acquired immune deficiency syndrome (AIDS) has been a global crisis and a big challenge plaguing the healthy living of humans today. It erodes both social and economic development as a result of its great influence on family stability, life expectancy and economic development. [1]

Globally HIV remains a major health challenge, with an estimate of 36.9 million people living with it at the end of 2014. Approximately 2 million people were newly

infected in 2014. While new cases have been reported in all regions of the world approximately 70% are in sub-Saharan Africa.[2] The total number of people living with HIV/AIDS in India was estimated at around 20.9 lakh in 2011, The four high prevalence states of South India including Tamilnadu account for 53% of all HIV infected population in the country.[3]

Highly active antiretroviral therapy (HAART) is a combination of at least three drugs for HIV-1 infection and the drugs are administered lifelong. Clinical benefits of

HAART are due to its effectiveness in decreasing disease progression in HIV infected patients by sustained suppression of viral replication. These benefits however are not without unwanted effects. Most of the drugs which are available and approved for use in HAART have some or the other adverse effects, thus treatment of HIV infection has become a complicated balancing act between the benefits of durable HIV suppression and the risks of drug toxicity.

The nucleoside reverse transcriptase inhibitors (NRTIs) are associated with lactic acidosis, lipodystrophy and hyperlipidemia. While the non nucleoside reverse transcriptase inhibitors (NNRTIs) are associated with neuropsychiatric symptoms, rash, liver toxicity and lipid abnormalities. Protease inhibitors (PIs) are associated with gastrointestinal intolerance and glucose and lipid abnormalities. The entry inhibitor (Maraviroc) and the integrase inhibitor (Raltegravir) are new drugs used for treatment-naive and treatment experienced patients. Maraviroc is associated with bronchitis, nasopharyngitis and oesophageal candidiasis, while Raltegravir is associated with increased risk of myopathy and rhabdomyolysis.[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. About 25% of all patients discontinue their initial HAART regimes because of treatment failure, toxic effects or noncompliance with in the first eight months of therapy.[4] Adverse drug reactions may also result in diminished quality of life, increased physician visits, hospitalizations, and even death. In addition, they result in increased health care costs. Most of the toxicity/side effects can be adequately co-managed with efficient clinical monitoring at all levels of the health care system. Hence, monitoring and reporting of ADRs in HIV/AIDS patients receiving ART assumes great importance.

This prospective study in would be beneficial to the HIV infected patients on antiretroviral therapy with the ultimate goal of improving the tolerability and effectiveness of treatment by promoting the early recognition of potentially serious adverse effects and to assess the causality of ADRs. Based on these objectives of this study is to assess risk factors related to antiretroviral therapy induced ADR and to assess causality and Severity assessment of reported ADRs.

## 2. Material and methods

The present study is undertaken to monitor adverse drug reactions in HIV patients in Government Dharmapuri Medical College, Dharmapuri. Here we have assessed related risk factors and sociodemographic profile of ADRs to ART. Causality and severity assessment of reported ADRs is done.

This study was done as prospective observational study and was over 1 year from Jan 2020 to Dec 2020. 150 patients who fulfilled inclusion criteria during study period were evaluated. Patients were selected by Simple Random Sampling. After obtaining approval and clearance from the Institutional ethical committee, the subjects fulfilling inclusion and exclusion criteria were included in the study after obtaining written informed consent.

Patients who were diagnosed and confirmed cases of HIV on ART of either sex were included in the study. Patients not willing to give consent, with concomitant disorders like diabetes mellitus, hypertension was excluded. All demographic details were collected. As per NACO guidelines all patients were followed at 15<sup>th</sup> day, 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> and 6<sup>th</sup> month.

At follow up visit's patients underwent detailed clinical evaluation with special emphasis on any new symptoms that were observed after initiation of ART or worsening of the pre-existing symptoms. CD4 count was repeated at 6<sup>th</sup> month as per NACO guidelines. Causality assessment of ADRs was done by Naranjo algorithm[5] Severity assessment of ADRs was done by Hartwig & Seigel's Severity scale.[6] The collected data was analyzed by using SPSS Software. Data was entered in excel format, was analyzed by Descriptive statistics to calculate frequencies and percentages. Chi-square test was done to find association with categorical variables.

## 3. Results

In the study, a total of 150 HIV positive patients who were receiving Anti Retro Viral therapy from the nodal ART center were enrolled. A prospective observational study was conducted in HIV patients attending. Total 150 patients were included in the study and they were followed up over a period of 6 months for ADRs. Of the 150 patients, 56 (37.3%) patients experienced ADRs. Out of 150 patients, 76 were males and 74 were females and 27 were aged between 14-50 years, 19 were more than 50 years and only 4 were less than 14years. More patients were from urban locality. There was not much difference in educational status with 86 patients were illiterate and 64 patients were literate. Most common mode of transmission was hetero sexual and only four patients had vertical transmission.

Coming to CD4 count, 13 patients had level less than 50, 23 had levels between 51-100, 23 had CD4 count between 101-200, 42 per cent of patients had level from 201-350 and 11 patient had levels above 350. Most common regimen used was ZLN (Zidovudine+ Lamivudine+ Nevirapine) in 103 patients, whereas in other patients' regimens like ABLN, TIN, TLE, TLN were used. WHO

clinical staging was done and in our patients 126 was in stage 1, 2 in stage 2, 15 in stage 3 and 6 in stage 4.

In the present study, out of 150 study subjects 56 (37.3%) experienced ADRs. The study showed 29 (52%) males and 27 (48%) females experienced ADRs. Majority of the ADRs were seen in adult patients aged between 14-50 years comprising 86% of total ADRs followed by 12% in >50 years of age and only 2% in <14 years of age. The study showed non-agriculture laborer’s experienced more ADRs comprising 55.4% followed by Housewives (21.4%) and Agriculture laborer’s (14.3%). The patients residing in urban area (64.7%) showed more ADRs (22.7%) than those among the rural residents (14.7%).

In the study, majority of ADRs were reported in Heterosexual mode of HIV, transmission (98.2%) followed by vertical mode (1.8%).The study showed majority of ADRs were seen in married patients (89.29%).In the study Illiterates had experienced more ADRs (53.6%) than literates (46.4%).

The study showed majority of ADRs occurred during 2 weeks of treatment (82.14%) followed by 4 weeks (5.35%).In the WHO regimen ZLN group showed more ADRs (73.2%) follows ZLE (14.3%)and TLE (7.1%).

**Table 1: Correlation of ADRs with Regimen**

Regimen	ADRs	
	Number	Percentage
ABLN	0	0
TIN	0	0
TLE	4	7.1
TLN	3	5.4
ZLE	8	14.3
ZLN	41	73.2
Total	56	100

Out of the 150 patients, 33 (22%) had opportunistic infections. Among them 12(36.4%) had reported ADRs. The patients with pulmonary TB reported a greater number of ADRs (74.97%) followed by herpes infection (16.66%). Majority of patients were WHO staging-1(84%) of HIV infection & majority of ADRs occurred with WHO staging-1 of HIV infection comprising 87.5%.

**Table 2: System wise distribution of ADRs**

System	ADRs	
	Number	Percentage
CNS	12	21.4
GIT	15	26.8
Haematology	18	32.1
Renal	1	1.8
Skin	7	12.5
Miscellaneous	3	5.4
Total	56	100

The most common ADRs observed were Hematological 18 (32.1%), followed by GIT 15 (26.8%), CNS 12 (21.4%) and Skin 7 (12.5%). Majority of ADRs

(46.4%) were reported in patients with CD4 Counts 201 to 350 followed by 26.8% in patients with counts 101 to 200.

**Table 3: Causality assessment of ADRs by Naranjo assessment scale**

Causality Assessment	ADRs	
	Number	Percentage
Definitive	4	7.5%
Possible	34	60%
Probable	18	32.5%
Unlikely	0	0

According to Naranjo algorithm 50% of the reported ADRs were found to be possible, 37.5% were probable and only 12.5% were definitive. According to Hartwig and Seigel Scale 51.8% of the reported ADRs were found to be moderate, 48.2% were mild.

#### 4. Discussion

The introduction of highly active antiretroviral therapy (HAART) has led to a significant reduction in AIDS-related morbidity and mortality.[7] Unfortunately, up to 25% of patients discontinue their initial HAART regimen because of treatment failure, toxic effects or noncompliance within the first 8 months of therapy. While development of new antiretroviral agents continues, efforts to maximize the effectiveness of currently available treatments include attempts to better understand and manage adverse effects. Because adverse events are common with all available antiretroviral agents, it is critical to anticipate, recognize and manage them when providing primary care for HIV infected patients.

This prospective, study was conducted on 150 HIV patients on treatment with the following anti-retroviral (ART) regimens. [1]

Zidovudine+Lamivudine+Nevirapine(AZT+3TC+NVP), Zidovudine+Lamivudine +Efavirenz (AZT+3TC+EFV), Tenofovir+ Lamivudine +Efavirenz(TDF+3TC+EFV), Tenofovir+Lamivudine +Nevirapine (TDF+3TC+NVP), Abacavir + Lamivudine + Nevirapine(ABC+3TC+NVP).

In the present study all the events which were suspected to be adverse effects were monitored. The patients recruited for the study fulfilled the inclusion and exclusion criteria. It was observed that, 37.3% of patients experienced ADRs to ART during the study period. In a study conducted by Luma *et al*[8] 19.5% ADRs were reported, whereas a study by Rajesh *et al*[9] reported 43.85% of ADRs which was high as compared to our study. These variations in the incidence rate of ADRs may be because of concurrent medications used for treating opportunistic infections and other co-morbid conditions which may result in increase of ADRs incidences.

ADRs was high among patients with WHO Clinical stage I constituting 87.5% in our study. Similar study by Divakar *et al*[10] reported adverse drug reactions among patients with WHO Clinical stage I & II was 26.5%, while in the stage III & IV was 21.9%. ADR to ART may depend on the baseline CD4+ cell count at initiation of therapy. In our study ADRs were 46.4% when HAART regimen was started with baseline CD4 Count 201-350 cells/mm<sup>3</sup>. Similar study conducted by Rajesh *et al*[9] showed ADRs to be 79.8% when CD4  $\leq$  200 cells/mm<sup>3</sup>.

In our study, age group of 14-50 years has been affected with more ADRs to ART. Study from Kadapa[11], India showed age group of 31-40 years were more affected. All these studies indicate that sexually active age group is more affected. Our study also showed 98.2% ADRs were due to Heterosexual mode of transmission compared to 1.8% by vertical mode. Our study also showed 89.29% of ADRs in married Patients.

In our study, incidence of ADRs to ART in males (51.7%) and females (48.1%) did not show any significant difference. A study by Lihite *et al*[12], showed the majority of ADRs were observed in males, as compared to female patients. The reasons for these sex differences in adverse drug reactions might be due to differences between men and women in body mass index and fat composition, hormonal effects on drug metabolism, or genetic constitutional differences on the levels of various enzymes.

In our study patients residing in urban areas showed more ADRs (22.7%) compared to those in rural areas. Illiterate patients showed more ADRs (53.6%) than literates in our study similar to the study by Modayil *et al*[13] which may be due to ignorance and lack of education regarding the disease.

ADRs were common with AZT + 3TC + NVP regimen comprising 73.2% followed by 14.3% with AZT + 3TC + EFV which may be attributable to larger number of patients receiving this combination. The study by Kennath<sup>14</sup> reported that ADR was less likely to occur in patients on stavudine-based and tenofovir-based regimens compared to zidovudine-based regimens. A study from Chhattisgarh showed stavudine (d4T) + 3TC +NVP was the most common regimen which caused ADRs.[15]

Majority of ADRs from our studies were Hematological (32.1%). Similar study conducted by Luma *et al*[8] showed 3.8% of hematological ADRs of which anemia was the most common and the most severe, all of which were associated with AZT-containing regimens. Zidovudine causes bone marrow suppression leading to anemia and thrombocytopenia. Agarwal *et al*[16] reported high incidence of Zidovudine-induced anemia in HIV-infected patients in eastern India.

GIT disturbance was the next affected ADR (26.8%) which included nausea, vomiting, gastritis, and abdominal pain. In a study by Lihite *et al* [12] 31.25% ADRs were related to gastrointestinal system. Most of the Gastrointestinal ADRs were observed in the first few weeks of therapy and symptoms were self-limiting.

CNS adverse effects were next common in our study comprising 21.4% of total ADRs which mainly consists of depression, giddiness and numbness. A study by Lihite *et al*[12] showed 16.25% ADRs which were related to central nervous system. The use of Efavirenz was observed as a risk factor.

Rashes 12.5% were seen with the NVP based regimen. Sharma *et al* [10] reported rashes in 10% of their study population. Other ADRs were renal 1.8% and miscellaneous (fatigue and fever) 5.4%.

Causality assessment using standard methods is one of the best ways to establish the causal relationship between a drug and its effects. In our study causality assessment was done using Naranjo causality assessment scale,[5] according to which 60% were 'possible' ADRs, 32.5% were 'probable' ADRs and 7.5% were 'definite' ADRs.

In a study done by Anshu Kumar[17] revealed 66.04% ADRs were 'probable' and 33.96% were 'possible'. These results are in contrast to the study conducted by Rajesh *et al*[9] where majority of ADRs (63.5%) were probable.

In order to take proper initiatives towards the management, severity of the ADRs is assessed by using Hartwig Siegel scale.[6] Among 56 ADRs in our study, 48.2% were mild and 51.8% were moderate in severity, whereas in a study done in Kadapa by Srikanth *et al*[11] 90.14% of ADRs were moderate in severity and 9.85% mild ADRs.

## 5. Conclusion

ADRs are more likely to occur during early treatment period and close monitoring is required to prevent occurrence of complications. Patients initiating Zidovudine containing HAART regimen are at a greater risk of developing ADRs compared with Tenofovir regimen. Therefore, future efforts should attempt to initiate more patients on Tenofovir-containing regimens that are supposed to be less toxic, which may decrease the number of ADRs in patients. So, ADRs among the patients with ART regimen is a critical public health issue for ARV treatment adherence and continuous monitoring is required to prevent severe ADRs and to improve patient compliance.

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