

**A Study on the Evaluation of Adverse Drug Reactions Associated with Antiretroviral Therapy in Tertiary Care Hospital****Kaushal Kumar Mishra<sup>1</sup>, Ashoka Kumar Chowdhury<sup>2</sup>, Satyendra Kumar Pathak<sup>3</sup>**<sup>1</sup>Assistant Professor, Department of Pharmacology, Sri Krishna Medical College, Muzaffarpur, Bihar.<sup>2</sup>Assistant Professor, Department of Pharmacology, Sri Krishna Medical College, Muzaffarpur, Bihar.<sup>3</sup>Professor & Head, Department of Pharmacology, Sri Krishna Medical College, Muzaffarpur, Bihar.

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Conflict of interest: Nil

**Abstract:****Objectives:** The present study was to evaluate the sociodemographic profile of HIV patients and adverse drug reaction in HIV patients with antiretroviral therapy in tertiary health care centre of Bihar, India.**Methods:** Socioeconomic status (SES) of the patients were assessed by Modified Kuppaswamy score. Drug reactions like anaemia, skin rashes, lipodystrophy and nephrotoxicity were diagnosed by routine investigations (CBC, RFT, LFT, Viral load) done during the regular follow up. Reactions like giddiness and peripheral neuropathy were described by patients during the visit.**Results:** A total of 150 diagnosed cases of HIV were included. Most of the cases 80(53.33%) were in age group of 31-43 years. And 100(66.66%) HIV cases were males. most of the patients 93(62%) were belonged in lower middle class. 73 (48.66%) cases had shown adverse drug reaction with ART. Among (73) them cases had 36(49.31%) anaemia, 17(23.28%) nephrotoxicity, 9(12.32%) skin rashes, 5(6.84%) giddiness, 4(5.48%) peripheral neuropathy and 2(2.73%) lipodystrophy. Anaemia being the most common drug reaction was associated with the zidovudine-based regimen. Tenofovir was associated with the development of nephrotoxicity.**Conclusions:** Most common adverse reaction of ART associated with zidovudin based regimens is anaemia. Second common ADR are nephrotoxicity, skin rashes, giddiness and peripheral neuropathy. And lower middle class socioeconomic strata and middle age male population are more preponderance for HIV infection.**Key words:** ADRs, ART, Sociodemographic profile, Zidovudin.This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.**Introduction**

Adverse drug reactions (ADRs) account for considerable mortality and morbidity besides having immense economic impact on patients, health-care providers and society. Most of the ADRs are preventable [1]. The incidence of ADRs among patients on antiretrovirals from both developing and developed countries ranges between 11% and 35.9% [1, 2] with incidence being as high as 54% coexistent with opportunistic infection [3]. Highly Active Anti-Retroviral Therapy (HAART) has made a significant change in the lives of people living with HIV (PLWH) in decreasing AIDS-related deaths and improving quality of life [4]. Despite their remarkable contribution, these drugs have been associated with serious adverse drug reactions (ADRs) that may lead to drug resistance and switching of anti-retroviral therapy (ART) regimen [5] and emergence of new comorbidities which may lead to decreased adherence consequently leading to virological failure [6]. It has been elucidated that the type of ART regimen influences the timing, nature and duration of ADRs [7]. Furthermore, the

occurrence of ADR might be higher in developing countries due to higher prevalence of concomitant conditions, overstretched healthcare systems and economic constraints that would hamper close follow up of patients on HAART [8]. Moreover, age, gender and the disease itself have been identified as risk factors for ADRs of HAART in different countries [9].

Antiretrovirals, like most chronically administered drugs, are reported to have adverse reaction and particularly higher occurrences are seen at the beginning of ART [10]. Moreover, long term adverse effects such as lipodystrophy and neuromotor disorders may be encountered in latter stages of treatment [10]. Not only this, studies also showed that ADRs could be a source for new comorbidities and hospital admission [11,12]. ADRs due to antiretrovirals can range from mild gastrointestinal disturbance [13] to serious adverse effects including hematological disorders [12], hepatotoxicity [14] and lactic acidosis [14]. Antiretrovirals mainly suppress viral load, thus

restoring the immune function. Declining costs of antiretrovirals along with the production of drugs by generic manufacturers has helped tertiary care hospital in resource-limited areas cater better antiretroviral care to HIV-seropositive population [15]. Despite showing considerable efficacy in reducing mortality and morbidity in PLHIV, ART is also associated with wide range of potential adverse effects leading to reduction in patient's quality of life and adversely affecting treatment adherence which may consequently lead to treatment failure. Adverse drug reactions (ADRs) to these medications remain a significant point of concern which may subsequently compromise the effectiveness of an ART program [3].

In India, the National AIDS Control Organization (NACO) publishes guidelines regularly, outlining the steps for diagnosis and treatment of HIV infection, the most recent ones being those published in 2013 [16]. According to these guidelines, the ideal time to start ART is before the patient presents with an opportunistic infection [16, 17]. Objectives of our study was to evaluate the sociodemographic profile HIV patients and adverse drug effects in HIV patients with antiretroviral therapy in tertiary health care centre of Bihar, India.

### Material & Methods

This present study was conducted in Department of Pharmacology with the collaboration of Department of ART, SKMCH, Muzaffarpur, Bihar during a period from February 2022 to December 2022. Entire subjects signed an informed consent approved by institutional ethical committee, of SKMCH, Muzaffarpur was sought.

A total of 150 diagnosed cases of HIV infection based on various clinical features and laboratory

investigations were enrolled in this study. All the participants had age group  $\geq 18$  years. These data were obtained about the basic demographic details, diagnosis, duration of illness and treatment, current treatment regimen, per-capita family income, side effect due to drugs, whether the drug was stopped after the side effect and patient was treated as out-patient or was admitted in the hospital.

- Socioeconomic status (SES) of the patients were assessed by Modified Kuppaswamy score. According to this Score, upper class: 26-29, upper middle class: 16-25, lower middle class: 11-15 and upper lower class: 5-10.
- Drug reactions like anaemia, skin rashes, lipodystrophy and nephrotoxicity were diagnosed by routine investigations (CBC, RFT, LFT, Viral load) done during the regular follow up. Reactions like giddiness and peripheral neuropathy were described by patients during the visit. During the course, Causality assessment of the reactions was done by WHO causality assessment scale and modified Hartwig and Siegel's scale was used for severity assessment. Once the ART drug causing the drug reaction was identified, the offending agent was stopped, and the regimen was changed.

### Statistical Analysis

Data was analysed by using simple statistical methods with the help of MS-Office software. All the data were tabulated and percentages were calculated.

### Observations

A total of 150 diagnosed cases of HIV were included in this study. Most of the cases 80(53.33%) were in age group of 31-43 years. And 100(66.66%) HIV cases were males.

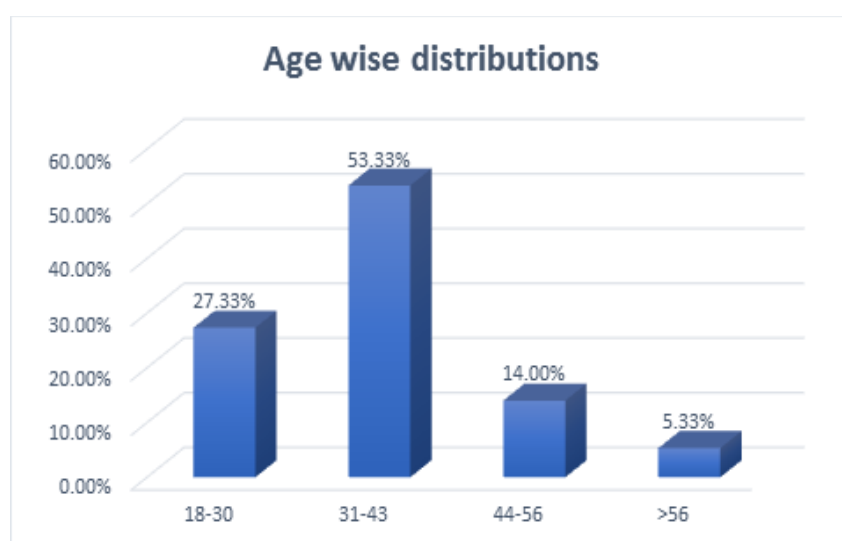


Figure 1: Age wise distributions of the patients.

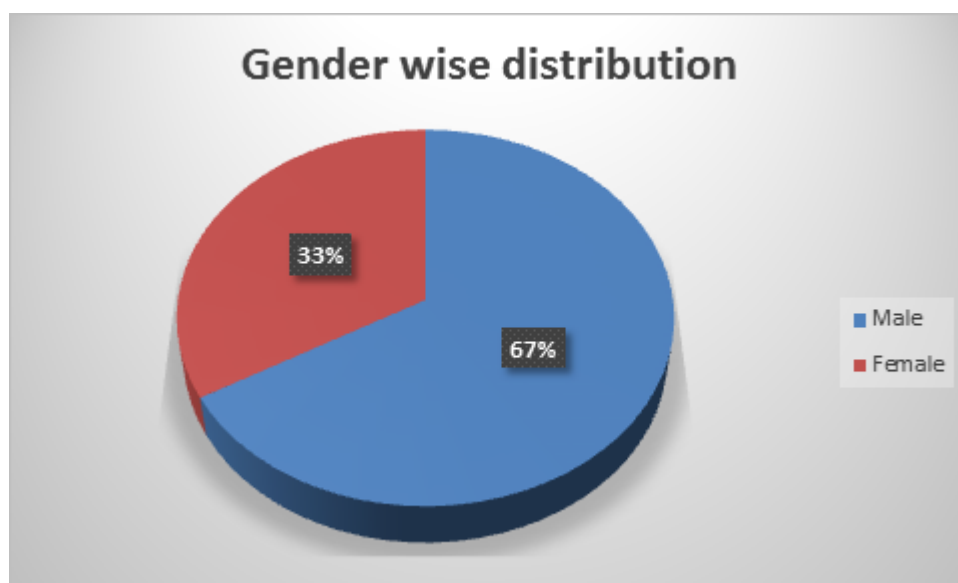


Figure 2: Gender wise distributions of the patients.

Table 1: Showing the socioeconomic status of the patients.

Modified Kuppaswamy score.	No. of patients	Percentages
26-29	0	0
16-25	0	0
11-15	8	5.33%
5-10	93	62%
>5	49	32%

On the basis of modified Kuppaswamy scale, most of the patients 93(62%) were belonged in lower middle class and had 5-10 score.

Table 2: Adverse drug reaction

ADR	No. of patients	Percentages
Anaemia	36	49.31%
Giddiness	5	6.84%
Peripheral neuropathy	4	5.48%
Lipodystrophy	2	2.73%
Skin rashes	9	12.32%
Nephrotoxicity	17	23.28%
Total	73	100%

Out of 150 cases, 73 (48.66%) cases had shown adverse drug reaction with ADR. Among (73) them cases had 36(49.31%) anaemia, 17(23.28%) nephrotoxicity, 9(12.32%) skin rashes, 5(6.84%) giddiness, 4(5.48%) peripheral neuropathy and 2(2.73%) lipodystrophy.

Table 3: ART drugs cause adverse reactions

*Classes	ART Drugs	Types of ADR	Treatment
NRTI	Zidovudine	Anaemia	Stopped
NNRTI	Efavirenz	Giddiness	Stopped
PI	Atazanavir	Peripheral neuropathy	Stopped
NRTI	Stavudine	Lipodystrophy, peripheral neuropathy	Stopped
NNRTI	Nevirapine	Skin rash	Stopped
NTRTI	Tenofovir	Nephrotoxicity	Stopped

\*Various classes of anti-retroviral drugs – NRTI – Nucleoside Reverse Transcriptase Inhibitors; NNRTI – Non nucleoside Reverse Transcriptase Inhibitors; PI – Protease Inhibitors; NTRTI – Nucleotide Reverse Transcriptase Inhibitors.

During the treatment, various ART drugs like Zidovudine, Efavirenz, Atazanavir, Stavudine, Nevirapine and Tenofovir were found to be associated with adverse reactions. Anaemia being

the most common drug reaction was associated with the zidovudine-based regimen. Tenofovir was associated with the development of nephrotoxicity. Skin rashes were observed with nevirapine use. Efavirenz was associated with giddiness. Atazanavir and Stavudine were associated with peripheral neuropathy. Case of lipodystrophy with stavudine use was reported only in 2(2.73%) patients.

### Discussions

Antiretroviral therapy (ART) has proved efficacious in reducing mortality and morbidity related to Human Immunodeficiency Virus (HIV) infection; [18] it is also associated with both short- and long-term drug-induced toxicities. These toxicities may reduce patient's quality of life and adversely affect treatment adherence; [19] and consequently may lead to treatment failure. Most of the ADRs are preventable. The incidence of ADRs among patients on antiretrovirals from both developing and developed countries ranges between 11% and 35.9% [20,21] with incidence being as high as 54% coexistent with opportunistic infection [16]. In the present study, prevalence 80(53.33%) of HIV was greatly seen in age group of 31-43 years. Males 100(66.66%) were more preponderance than females 50(33.33%). Anti-retroviral therapy (ART) has improved the prognosis for people living with HIV-infection/acquired immunodeficiency syndrome (AIDS) (PLHA).

In Nigeria, there are 359, 181 patients receiving ART as of December 2010 in over 200 secondary and tertiary hospitals, with plans to decentralize to primary health care level. [22] However, information regarding the occurrence and types of adverse drug reactions (ADRs) in these patients is very limited. Epidemiologic data support the existence of specific factors that increase the risk of general ADR, such as female gender [23]. The incidence of severe ADRs was 32.55% in patients 35 years of age, though the difference was not statistically significant [24]. On the contrary, Eluwa et al. reported that age and gender were not significantly associated with ADRs [25]. Antiretrovirals, like most chronically administered drugs, are reported to have adverse reaction and particularly higher occurrences are seen at the beginning of ART [26]. Moreover, long term adverse effects such as lipodystrophy and neuromotor disorders may be encountered in latter stages of treatment [26]. Not only this, studies also showed that ADRs could be a source for new co-morbidities and hospital admission [27]. ADRs due to antiretrovirals can range from mild gastrointestinal disturbance [30] to serious adverse effects including hematological disorders [27], hepatotoxicity [28] and lactic acidosis [28]. A study done in Brazil among patients initiating ART in the first six month of therapy showed that at least one adverse reaction was reported by 92.2% of the participants while 56.2%

reported four or more different reactions [22]. Singh et al. reported that 86% of patients had at least one ADR, of which, the most common observed was peripheral neuropathy [29]. A prospective observational study by Nagpal et al. reported that about 90% of patients experienced ADR [30]. In the present study. Prevalence of ADRs with ATR was 48.66%. Most common adverse reaction was anaemia 36(49.31%). Others ADRs were 17(23.28%) nephrotoxicity, 9(12.32%) skin rashes, 5(6.84%) giddiness, 4(5.48%) peripheral neuropathy and 2(2.73%) lipodystrophy. Numerous reports have documented rash with ART therapy mainly with nevirapine [31]. Drug hypersensitivity in form of rash occur with HAART therapy usually in first 6 weeks of therapy [32]. Nevirapine, delavirdine and efavirenz, abacavir, amprenavir cause rashes frequently due to hypersensitivity which usually resolve spontaneously [31]. In this present study, Peripheral neuropathy was seen in 4(5.48%) cases. Peripheral neuropathy is mainly seen with atazanavir and stavudine [33]. These inhibit nerve growth factor and result in neuropathy 1.3–22.3% of prevalence has been documented [34].

The success of the anti-retroviral treatment is highly dependent on the motivation of HIV positive individuals to adhere to complex ART [35] regimens. Unfortunately, up to 25% of patients discontinue their initial HAART regimen because of toxic effects, noncompliance or [36] treatment failure within the rest 8 months of therapy. The occurrence of [37] side effects can vary dramatically among different people. Continuous evaluation needs to be done for the benefit of ART help to achieve the ultimate goal of making safer and more effective treatment to the patients [38].

There has been reduction in mortality with increased use of potent antiretroviral drugs generally administered in a combination of three or four agents [35]. Most of the drugs available and approved for use in highly active antiretroviral therapy (HAART) have some or the other adverse effects. Serious side effects are more varied with nucleoside analogs (zidovudine, didanosine, stavudine, lamivudine, tenofovir, etc.) including mitochondrial damage that can lead to lactic acidosis as well as peripheral neuropathy and pancreatitis. HAART therapy has also been associated with lipodystrophy syndrome of hyperlipidemia and fat redistribution [36]. Among the other side effects are fatigue, malaise, nausea, anemia, and hepatotoxicity. Non-nucleoside inhibitors, nevirapine and efavirenz are used in combination with nucleoside analogs for the treatment of HIV and are associated with the development of a maculopapular rash, dizziness, feeling of light headedness [35,36].

ADRs become a concern and public health problem particularly in developing nations as adequate drug toxicity monitoring and reporting schemes barely

existed. Lack of ADR monitoring and reporting system underestimates the burden of ART associated ADRs. Therefore, this ADR studies could be one way of addressing such gaps.

### Conclusions

This present study concluded that the most common adverse reaction of ART associated with ziduvudin based regimens is anaemia. Second common ADR are nephrotoxicity, skin rashes, giddiness and peripheral neuropathy. And lower middle class socioeconomic strata and middle age male population are more preponderance for HIV infection.

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