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ADVERSE DRUG REACTIONS WITH ANTIRETROVIRAL THERAPY: HIV/AIDS PATIENTS VISITING ANTIRETROVIRAL THERAPY CENTRE AT GOVERNMENT MEDICAL COLLEGE PATIALA.

Pharmacology

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ABSTRACT

Antiretroviral therapy are associated with wide range of potential adverse drug reactions. These are mostly manageable and tolerable, however it is not uncommon to have patients with negative impact on quality of life due to drug related toxicity. This leads to decreased compliance, which is a major cause of treatment failure. The present study was designed to evaluate the adverse drug reactions profile in HIV patients on two most commonly prescribed antiretroviral therapy regimen visiting ART centre at Government medical college Patiala.

KEYWORDS

Adverse drug reactions, antiretroviral therapy regimens, human immunodeficiency virus.

INTRODUCTION

In the last 30 years, the human immunodeficiency virus (HIV) pandemic has emerged as one of the major challenges for the world. From the first reported case in the early 1980s, to an estimated high of 3.7 million new infections in late 90's and to declining new infections and acquired immune deficiency syndrome (AIDS)-related mortality seen in recent years. [1, 2] As per recent statistics by World health organisation (WHO) 36.9 million people were living with HIV/AIDS worldwide in 2017.[3] In India total number of people living with HIV is estimated to be 21.40 lakhs according to 2017 National AIDS Control Organisation (NACO) report. [4] Among the Indian states/union territories Manipur has highest estimated HIV prevalence followed by Mizoram, Nagaland, Andhra Pradesh and Telangana. Estimated adult HIV prevalence in Punjab is 0.19 %.[4,5]

Advancements in healthcare and improved accessibility has led to reversal of the global trend for new infection and AIDS related morbidity and mortality. Recent WHO statistics reported 59% people living with HIV were on antiretroviral therapy (ART). [6] There were 528 anti-retro viral therapy (ART) centres established until September 2016 in India. These centres provide facilities for HIV testing, drug therapy and psychological counselling. India also launched Link Work Scheme to connect rural communities to HIV programmes and provided them access to existing services, with special focus on high risk population and other vulnerable groups.[4,7]

Antiretroviral therapy is highly efficacious in decreasing viral load that improves immune function and decreases incidences of opportunistic infection. Adherence to the ART is critical for optimal response and to minimize the risk of developing drug resistance.[8] In the earlier era of combination ART the adverse effects were among the most common reasons for non-compliance, which causes treatment failure. Fortunately, newer ART regimens have better toxicity profile and tolerability. This results in improved patient compliance and sustained viral suppression for much longer time.[9]

This study was conducted to evaluate the adverse drug reactions (ADR) profile of ART regimens in HIV patients visiting nodal ART Center at government medical college Patiala, Punjab. The study is registered at www.ctri.nic.in, registration number for the study is CTRI/2019/02/017398.

AIMS & OBJECTIVE

To evaluate the adverse drug reactions (ADR) due to antiretroviral therapy (ART) in HIV/AIDS patients.

MATERIALAND METHOD

The ethical approval for this study was obtained from the ethics committee of Government Medical College Patiala. Written informed consent was obtained from all subjects. Confidentiality was assured by excluding patients' identifier during analysis.

This was a cross-sectional, observational study conducted over a period of 6 months, conducted at nodal ART Centre of government medical college, Patiala. 100 HIV/AIDS who met the inclusion criteria were enrolled in the study, with probability α error of 5% and keeping power of study at 80%.

Key Inclusion criteria

1. Diagnosed cases of HIV, both Female and Male,
2. Patient willing to give written informed consent.

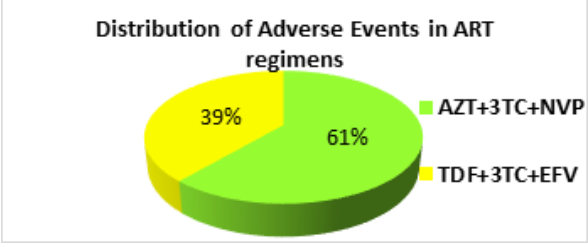
Key Exclusion criteria

1. Patients with known hypersensitivity to any ART drug,
2. CD4 count below 200µl/mm^3

RESULTS

Total of 100 subjects were enrolled in the study. The mean age of subjects enrolled was 41.42±11.09 years. The maximum number of subjects were of age group of 31-40 years. There were 51% female and 49% male patients enrolled in the study. The most common ART regimes prescribed was TDF+3TC+EFV (Tenofovir + Lamivudine + Efavirnez), 42 patients and AZT+3TC+NVP (Zidovudine + Lamivudine + Nevirapine), 58 patients. There were total 44 adverse events (AE) reported in 100 subject. Out of 44 AEs observed 27 (61%) AEs were observed in TDF+3TC+EFV and 17 (39%) AEs were observed in AZT+3TC+NVP group. TDF [Figure 1]

Figure 1: Distribution of Adverse Events in ART regimens

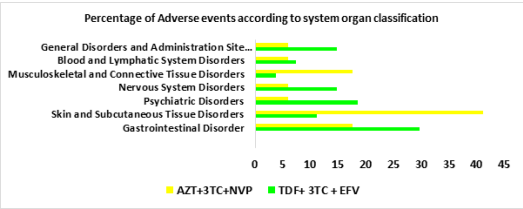


The most common AEs observed with TDF+3TC+EFV regimen system organ classification (SOC) wise included gastrointestinal disorder (29.63%) followed by Psychiatric disorders (18.52%), nervous system disorders and general disorders and site administration condition (14.82% each), skin and subcutaneous disorders (11.11%), blood and lymphatic disorders (7.41%) and lastly musculoskeletal and connective tissue disorders (3.70%).

The most common AEs observed with AZT+3TC+NVP regimen SOC wise included skin and subcutaneous tissue disorders (41.17%) followed by Musculoskeletal and connective tissue disorders and gastrointestinal disorder (17.64%), psychiatric disorder, nervous system disorder, blood and lymphatic disorders and general disorders

and site administration condition (5.88% each). [Figure 2].

Figure 2 : Percentage of adverse events observed according to system organ classification (SOC)



The most common AEs observed with TDF+3TC+EFV regimen preferred term wise included Anxiety (18.52%) followed by abdominal discomfort and gastritis (11.11% each), flatulence, malaise, decreased appetite, pruritus, anaemia, dizziness and peripheral neuropathy (7.41% each). [Table 1]

The most common AEs observed with AZT+3TC+NVP regimen preferred term wise included pigmentation disorders (35.29%) followed by Back pain and gastritis (11.76% each), pruritus pain in extremities, nausea/vomiting, depressed mood, peripheral neuropathy and anemia (5.88% each). [Table 1]

Table 1: Percentage and Frequency of Adverse event observed with ART regimen according to preferred term

	TDF+ 3TC + EFV (N=27)		AZT+3TC+NVP (N=17)	
	Frequency	Percentage	Frequency	Percentage
Gastrointestinal disorder				
Abdominal discomfort	3	11.11%	0	0%
Gastritis	3	11.11%	2	11.76%
Flatulence	2	7.41%	0	0%
Nausea/Vomiting	0	0%	1	5.88%
Skin and subcutaneous tissue disorders				
Rash	1	3.70%	0	0%
Pruritus	2	7.41%	1	5.88%
Pigmentation disorder	0	0%	6	35.29%
Psychiatric disorders				
Anxiety	5	18.52%	0	0%
Depressed mood	0	0%	1	5.88%
Nervous system disorders				
Dizziness	2	7.41%	0	0%
Neuropathy peripheral	2	7.41%	1	5.88%
Musculoskeletal and connective tissue disorders				
Pain in extremity	1	3.70%	1	5.88%
Back pain	0	0%	2	11.76%
Blood and lymphatic system disorders				
Anaemia	2	7.41%	1	5.88%
General disorders and administration site conditions				
Malaise	2	7.41%	1	5.88%
Decreased appetite	2	7.41%	0	0%
Total	**27**	**100%**	**17**	**100%**

DISCUSSION

Spontaneous reporting method of ADRs is the foundation of our national drug safety evaluation which is administratively simpler, covers population, and identifies rare adverse events.[10]

This study analysed the pattern of spontaneously reported ADRs in different drug regimens prescribed at a nodal ART centre, Punjab. The two most commonly used regimes were TDF+3TC+EFV and AZT+3TC+NVP. In accord with present study Chauhan et al reported that the most commonly prescribed regimens were TDF+3TC+EFV and AZT+3TC+NVP at their ART centre.[11] In the present study out of the two prescribed ART regimens more patients were on AZT+3TC+NVP regimen. WHO 2013 recommends to initiate ART with TDF+3TC+EFV and to start AZT+3TC+NVP if former is contraindicated. However it is not uncommon to prescribe AZT+3TC+NVP regimen as first choice, in accord to study conducted by Dubey S et al .[12, 13] Additionally NACO recommendations include Zidovudine based therapy as first regimen and Tenofovir based therapy as second regimen .[14]

In present study total 44 AEs were observed in 100 subjects. Higher number of AEs were observed patients on TDF+3TC+EFV regimens as compared to patients on AZT+3TC+NVP regimen. This is in contrast to studies conducted by Chauhan et al and Jain et[11,15] the two studies reported more AE occurred with AZT+3TC+NVP regimen.

In present study the most common AEs reported with TDF+3TC+EFV were gastrointestinal related [abdominal discomfort (3, 11.11%), gastritis (3, 11.11%) and flatulence (2, 7.41%)], followed by psychiatric disorders [anxiety (5, 18.52%)] and neurological disorder [dizziness and peripheral neuropathy (2, 7.41% each)]. This is consistent with another study conducted by Hemasri M et al[16] that reported most common ADR with TDF+3TC+EFV were gastrointestinal disorder related [Nausea (12%), vomiting (18%), diarrhoea (9%) and other GI related side effects(18%)] followed by neurological disorders [drowsiness (30%), headache (18%) and insomnia(6%)] and psychiatric disorders[depression (22%) and psychosis(6%)]. Sood et al[17] reported that maximum numbers of neurological AEs [(Dizziness, headache, insomnia, numbness, irritability, amnesia, confusion) (39.8%)] were reported with TDF+3TC+EFV regimen. Kenneth et al[10] reported that peripheral neuropathy is associated with tenofovir/emtricitabine/efavirenz regimen and close monitoring of patients receiving this regimen is very imperative.

Tenofovir is found to be mildly safer and it is the combination with efavirnez in the regimen that is cause of CNS side effects.[18] Consistent to the studies reported above the most common systemic presentation of neurological AE in present study for subject on TDF+3TC+EFV regimens was anxiety (18.52%) and lesser common neurological ADRs were dizziness and peripheral neuropathy.

For the patients on AZT+3TC+NVP regimens the most common AEs observed in present study were skin and subcutaneous tissue related pigmentation disorder [(6, 35.29%) and pruritus (1, 5.88%)], followed by musculoskeletal and connective tissue disorder back pain [(2, 11.7%) and pain in extremities (1, 5.88%)] and gastrointestinal related gastritis [(2, 11.76%) and nausea(1, 5.88%)]. Jaykare S C et al. [19] reported that most common AE with AZT+3TC+NVP are nausea/vomiting (57.90%), anaemia (55.56%) anorexia (48.15%) gastritis (46.67%) body ache (46.15%) and itching (44.44%). Kumari R et[20] al reported that most common AE with AZT+3TC+NVP regimens was anaemia followed by insomnia, rashes, headache and skin pigmentation. In contrast to studies cited above present study observed anaemia (1, 5.88%) less commonly. Zidovudine being a myelosuppressive drug is known to cause anaemia within 3 months of initiating therapy, which explains the high incidence of anaemia in Zidovudine based regimens.[21] Additionally present study reported over all higher incidence of pigmentation disorders (6, 35.29%). Mukherjee S et al[18] reported that nevirapine based regimens were associated with rash and pigmentation of nails (up to 55%). Sood et[17] reported that most common AEs with AZT+3TC+NVP regimens included haematological disorders [Dyslipidaemia, anaemia (22.9%)] followed by dermatological disorders [Pruritus, rashes, alopecia, SJ Syndrome, nail discoloration (20.5%)] and gastrointestinal disorders [Anorexia, deranged LFTs, nausea, vomiting, diarrhoea, oral ulcers (20.5%)], reported AEs pattern is similar to that observed in present study.

There is wide range of AEs associated with ART. The AEs related to ART depend on various factors like age, gender, duration of treatment, presence of co-morbid condition e.g., malnutrition, tuberculosis, stage of HIV, CD4 counts, class of drugs given. One of the challenges in managing these AE is that ART regimens come as fixed dose combinations of different drugs having varied toxicity profiles. This makes identification of toxicity to individual drug difficult and does not allow for individual drug dose interruption, reduction or discontinuation[22,23]

The strengths of the study were that it is based on active surveillance of clinical and laboratory parameters. There was minimal loss of data due to study design. Limitations of the study were that it majorly included patients who had initiated ART before active surveillance of AEs commenced this provided information more on long term adverse effects, we may have missed early onset ADR from these patients. The small sample size of patients on different regimen limits our ability to compare ADR reported by other studies with different regimes. The study may not be a representative of true AE detection rates as data was generated by spontaneous reporting system.

CONCLUSION

The study enables to obtain incidence and pattern of adverse drug reaction associated with antiretroviral regimens in HIV patients. Overall most common ADRs were gastrointestinal related, with gastritis being most common AE observed in the GI disorders. Skin and subcutaneous tissue disorder were second most common AE, with pigmentation disorder as the most common AE observed in this SOC.

Conflict of Interest

There is no conflict of interest. Author Dr. Ruchika Dillu was post graduate student when the present study was conducted and presently work with Sunpharma Advanced Research Company. There are no conflicting interest for the work then done by the author and her present affiliation.

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