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Analysis of Clinical Profile of Adverse Drug Reactions among Hiv Positive Patients on Antiretroviral Therapy

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ABSTRACT

Background- Acquired Immunodeficiency Syndrome (AIDS) is a disease of the human immune system caused by the Human Immunodeficiency Virus (HIV). This condition progressively reduces the effectiveness of the immune system and leaves individuals susceptible to opportunistic infections and tumors. Current ART regimens are capable of reducing viral load to undetectable levels with a consequent increase in CD4+ counts and a substantial reduction in HIV-associated morbidity and mortality. In spite of ART benefits, adverse reactions to these drugs have been pointed to as one of the main reasons for discontinuation and non-adherence to ART. Continuous evaluation of the benefit and harm of ART will help to achieve the ultimate goal of making safer and more effective treatment available to patients.
Objective- This study is being undertaken to analyse the clinical profile of various adverse drugs reactions due to antiretroviral therapy among HIV positive patients.
Methods- This is a prospective study conducted at Vijayanagar Institute of Medical Sciences Hospital, Ballari, period from February 2021 to August 2022. The participants were followed up at ART Plus Centre, and VIMS Hospital, Ballari for a total duration of 18 months. Relevant investigations were done to confirm the adverse reactions.
Results- Among 115 patients enrolled for the study the largest no. of patients was in the age group of 31-40 years (33.91%), followed by 21-30 years (23.48%). In the current study, out of 115 study participants, majority were female (59.13%) and male participants were 47(40.87%).
Conclusion- Antiretroviral therapy is becoming increasingly effective but also increasingly complex. The many adverse effects of therapy may cause symptoms affecting a variety of organ systems. Although current antiretroviral regimens are potent from an antiviral perspective, they often fail because of patient nonadherence.

Key Words: *Acquired Immunodeficiency Syndrome (AIDS), Human Immunodeficiency Virus (HIV), Antiretroviral Therapy(ART), Adverse drug reactions*

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INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). This condition progressively reduces the effectiveness of the immune system and leaves individuals susceptible to opportunistic infections and tumors [1].

HIV-AIDS, first recognized in the United States in the summer of 1981, was considered an incurable and terminal infection, till the development and availability of effective antiretroviral drugs. Development of these drugs and in particular their use as *combination* therapy have significantly improved the outcome in a patient infected with HIV [2].

Although treatments for AIDS and HIV can slow the course of the disease, there is no known cure or vaccine. Antiretroviral treatment reduces both the mortality and the morbidity of HIV infection, and current ART regimens are capable of reducing viral load to undetectable levels with a consequent increase in lymphocyte T-CD4+ counts and a substantial reduction in HIV-associated morbidity and mortality [1].

In spite of ART benefits, adverse reactions to these drugs have been pointed to as one of the main reasons for discontinuation and non-adherence to ART Success of the anti-retroviral treatment is highly dependent on willingness of HIV positive Individuals to adhere to complex ARV regimens [3]. Unfortunately, up to 25% of patients discontinue their initial HAART regimen because of toxic effects, noncompliance or treatment failure within the first 8 months of therapy [4].

Continuous evaluation of the benefit and harm of ART will help to achieve the ultimate goal of making safer and more effective treatment available to patients [5]. Therefore, many countries have adverse drug reactions (ADR)

monitoring centers, which are responsible for collecting, compiling and analyzing any ADRs information reported by health professionals. Based on this information, risk-benefit evaluation is made and safety measures are taken to protect the public from unnecessary harm.

Hence this study was aimed to analyse the clinical profile of adverse drug reactions among HIV positive patients on Antiretroviral Therapy.

METHODOLOGY

The present cohort prospective study was conducted on patients visiting ART Plus Centre, VIMS Ballari fulfilling the inclusion criteria, after obtaining approval and clearance from the institutional ethics committee. A total of 115 participants were selected after explaining the purpose of the study and procedure in detail and, after attaining their consent in written format for each patient. Demographic data, history, clinical examination and details of investigations were recorded in the study proforma. The history was collected by direct interview of the patient and patient relatives accompanying the patient.

All the participants were asked about any side-effects that they are experiencing and noted down in the study proforma. The participants were followed up after one month when they visited ART Plus Centre for issue of ART drugs, and subsequently every once in three months or whenever the patient visited VIMS, Hospital due to an adverse event. Relevant investigations were done to confirm the adverse reactions. The study was conducted for a total duration of 18 months. The collected data was entered in microsoft excel and analysed using statisitical package for social sciences (SPSS) version 24.0. Results are expressed using statistical parameters using mean, standard deviation, percentage wherever applicable. Tests for association was conducted using Chi-square test and p value less than 0.05 considered as statistically significant.

RESULTS

In the present study, maximum participants belonged to age group of 31-40 years (33.91%), followed by 21-30 years(23.48%).[Fig.1] Mean age is 38.45±11.37years. Out of 115 study participants, majority were female (59.13%)[Table 1]. Five different regimens were used for treatment in our study, each regimen containing two NRTIs and either Dolutegravir/Protease inhibitor drugs. Majority of 92 patients (80%) were on TLD Regimen, followed by 9 on ZL+DTG (7.8%). [Fig.2]

Among patients using TLD regimen (92), 26 had no adverse events, 20 had 1, 25 had 2-3 adverse events and 21 had more than 3 adverse events. Patients using ABC+L+DTG regimen (4), all of them had 2-3 adverse events. Patients using TL+ATV/r regimen (5), all of them had 2-3 adverse events. Patients using ZL+ATV/r, 5 of them had >3 adverse events and 9 of the patients on ZL + DTG regimen had more than 3 adverse events. [Table 3 and Fig.3]

Gastrointestinal adverse events were seen among 51 patients (44.35%), followed by 43 participants (37.39%) had metabolic adverse events. Allergic reaction was experienced by 22 patients (19.13%), 15 had CNS related reaction (13.04%), 15(13.04%) had hematological adverse events, and 44(38.26%) had other adverse events. [Table 4 and Fig.4]

GI adverse event Nausea was experienced by participants in all the five regimen. 19.57% among the 92 patients on TLD regimen experienced nausea, followed by heartburn in 14.13%, and loss of appetite in 11.96%. Major GI adverse event among patients on ZL+ATV/r was diarrhoea in 60%, followed by loss of appetite (40%) and nausea in 20%. 77.78% patients on ZL+DTG regimen experienced nausea. [Table 5 and Fig.5]

Among 9 patients on ZL+DTG, 6 patients (66.67%) developed anemia, and 4 patients (44.44%) developed leucopenia and thrombocytopenia. Out of 5 patients on ZL+ATV/r, 2 patients (40%) developed anemia and 1 patient (20%) had leucopenia. [Table 6 and Fig.6]

Among the derangements in metabolic parameters, Dyslipidemia was found to be present in 44.44% of patients on ZL+DTG regimen, followed by TLD regimen with 14.13%. Two patients (40%) of patients on TL+ATV/r regimen and five patients (5.43%) on TLD regimen developed lipohypertrophy. [Table 7 and Fig.7]

Among five patients on ZL+ATV/r regimen, 3 patients (60%) experienced headache, and two patients (40%) developed fatigue. Out of 92 patients on TLD regimen, 10.87% patients had fatigue, 9.78% patients experienced headache and myalgia. [Table 8 and Fig.8]

A total of 10 patients were on Cotrimoxazole Preventive therapy (CPT), out of which 9 patients (90%) developed rash, 7 patients (70%) developed allergic reactions and six patients (60%) developed metabolic adverse events. Among seven patients on both CPT and Isoniazid Preventive Therapy (IPT), all of them developed GI adverse events and six patients (85.71%) had metabolic adverse events. [Table 9 and Fig.9]

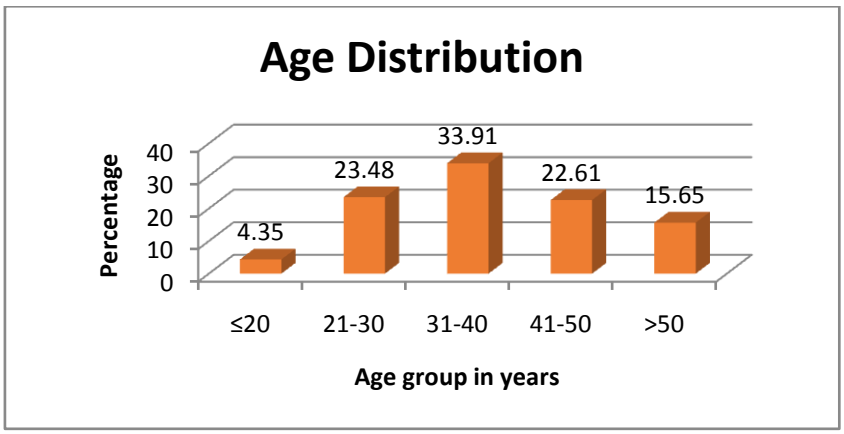

Figure 1: Distribution of participants according to age group

Table 1: Distribution of study participants according to Gender

Gender	Frequency	Percentage
Male	47	40.87
Female	68	59.13
Total	115	100.00

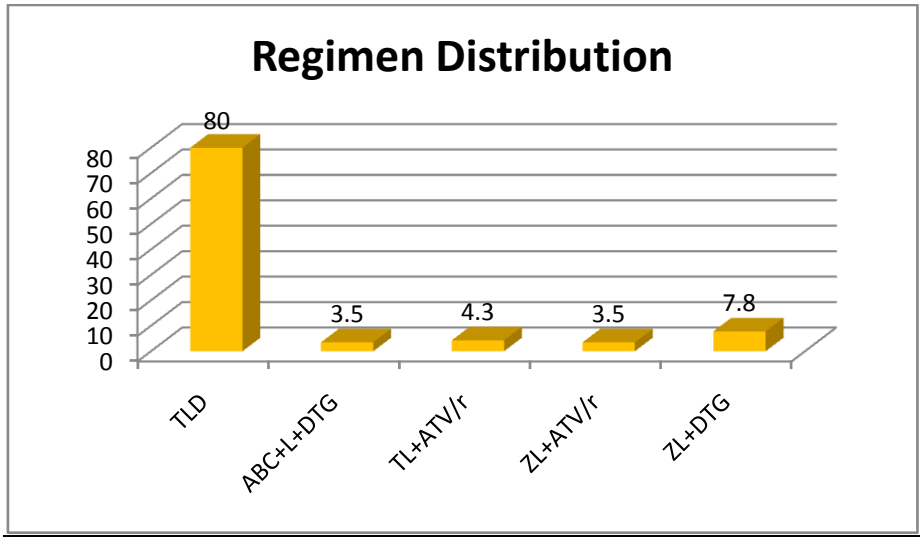

Figure 2: Distribution of ART Regimen

Table 2: Distribution of ART Regimen

Regimen	Frequency	Percentage
TLD	92	80.0
ABC+L+DTG	4	3.5
TL+ATV/r	5	4.3
ZL+ATV/r	5	3.5
ZL+DTG	9	7.8
Total	115	100.00

Table 3: Frequency of Adverse Events based on ART Regimen

Adverse Events	Regimen												P value
	TLD (92)		ABC+L+DTG (4)		TL+ATV/r (5)		ZL+ATV/r (5)		ZL+DTG (9)		Total		
	N	%	n	%	n	%	N	%	N	%	N	%	
Nil	26	28.26	0	0	0	0	0	0	0	0	26	22.61	0.18
1	20	21.74	0	0	0	0	0	0	0	0	20	17.39	0.30
2—3	25	27.17	4	100	5	100	0	0	0	0	34	29.57	0.02
>3	21	22.83	0	0	0	0	5	100	9	100	35	30.43	0.003

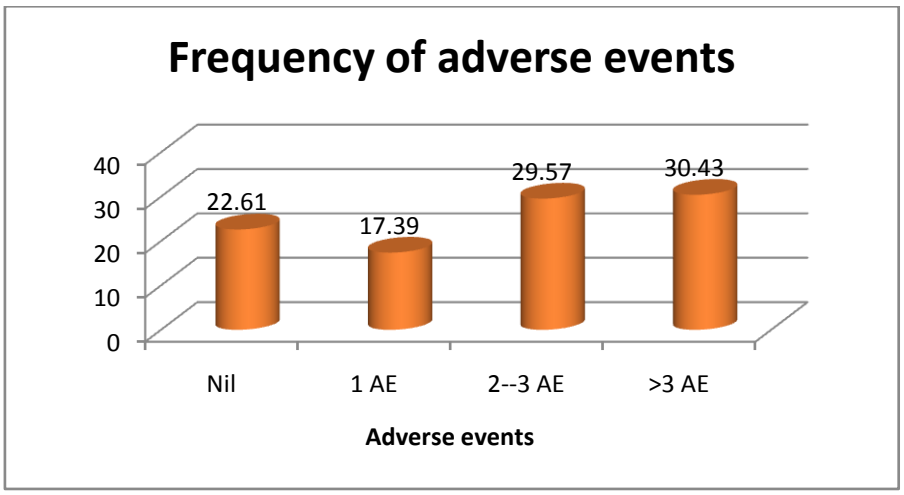

Figure 3: Frequency of Adverse Events based on ART Regimen

Table 4: Frequency distribution of occurrence of adverse events

Adverse events	Frequency	Percentage
GI	51	44.35
Allergic reaction	22	19.13
CNS	15	13.04
Hematological	15	13.04
Metabolic	43	37.39
Hyper pigmentation of skin and nails	0	0.00
Others	44	38.26

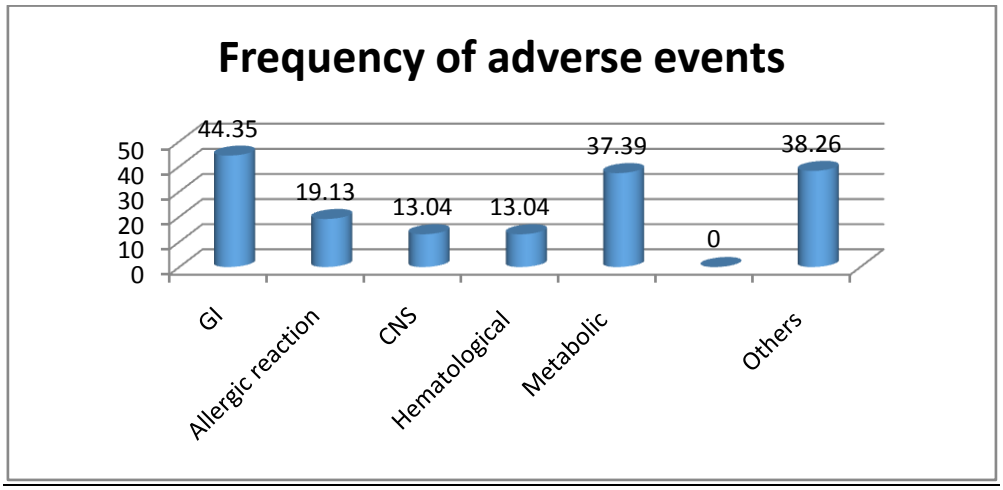

Figure4: Frequency distribution of occurrence of adverse events

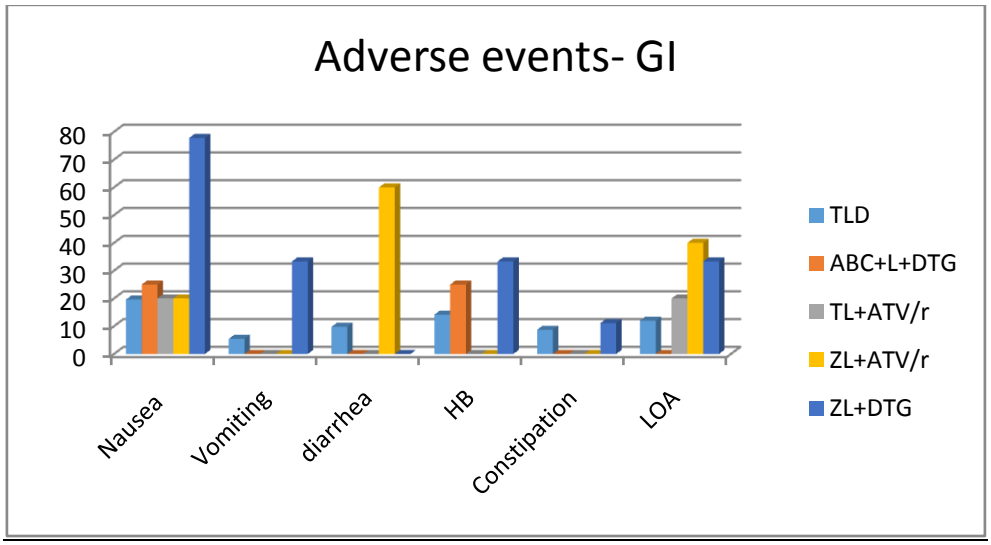

Figure 5: Adverse events-GI Distribution according to Regimen

Table 5: Adverse events-GI Distribution according to Regimen

Adverse events- GI	TLD (92)		ABC+L+DTG (4)		TL+ATV/r (5)		ZL+ATV/r(5)		ZL+DTG (9)		P value
	n	%	n	%	N	%	N	%	N	%	
Nausea	18	19.57	1	25	1	20	1	20	7	77.78	0.15
Vomiting	5	5.43	0	0	0	0	0	0	3	33.33	0.09
Diarrhea	9	9.78	0	0	0	0	3	60	0	0.00	0.05
Heartburn	13	14.13	1	25	0	0	0	0	3	33.33	0.51
Constipation	8	8.70	0	0	0	0	0	0	1	11.11	0.86
Loss of Appetite	11	11.96	0	0	1	20	2	40	3	33.33	0.37

Table 6: Distribution of Haematological adverse events according to Regimen

Adverse events- Hematological	TLD (92)		ABC+L+ DTG (4)		TL+ATV/r (5)		ZL+ATV/r (5)		ZL+DTG (9)		P value
	N	%	n	%	N	%	N	%	N	%	
Anemia	7	7.61	0	0	0	0	2	40	6	66.67	0.0001
Leucopenia	2	2.17	0	0	0	0	1	20	4	44.44	0.0007
Thrombocytopenia	2	2.17	0	0	0	0	0	0	4	44.44	0.0003

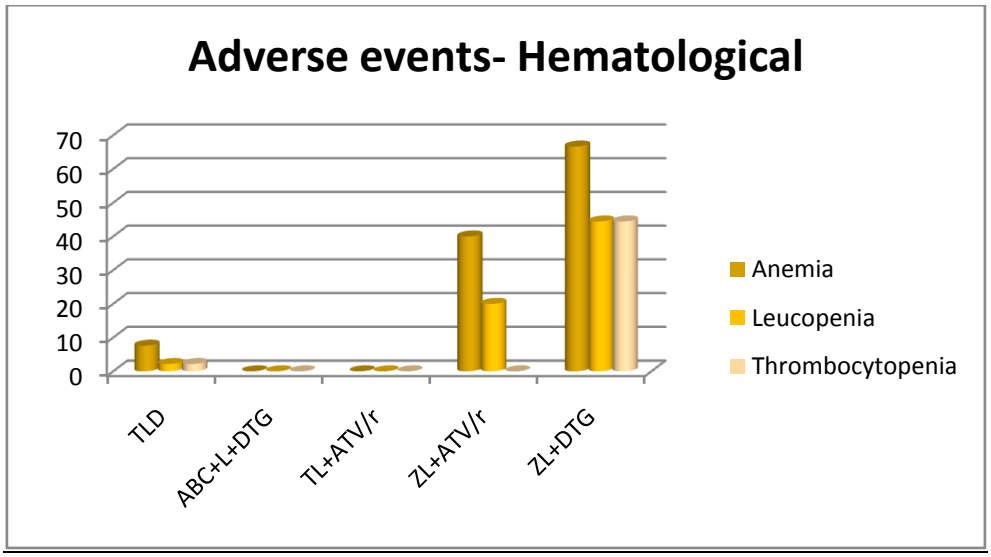

Figure 6: Distribution of Haematological adverse events according to Regimen

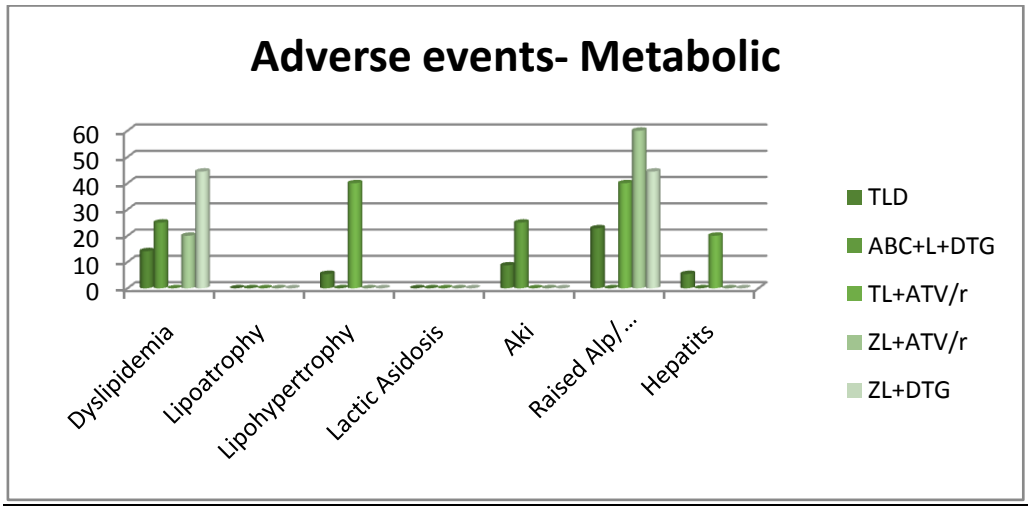

Figure 7: Adverse events-Metabolic according to Regimen

Table 7: Metabolic Adverse events according to Regimen

Adverse events- Metabolic	TLD (92)	ABC+L+DTG (4)	TL+ATV/r (5)	ZL+ATV/r (5)	ZL+DTG (9)	P value

	n	%	n	%	N	%	N	%	N	%	
Dyslipidemia	13	14.13	1	25	0	0	1	20	4	44.44	0.37
Lipoatrophy	0	0.00	0	0	0	0	0	0	0	0.00	-
Lipohypertrophy	5	5.43	0	0	2	40	0	0	0	0.00	0.09
Lactic Acidosis	0	0.00	0	0	0	0	0	0	0	0.00	-
AKI	8	8.70	1	25	0	0	0	0	0	0.00	0.59
Cholestasis	21	22.83	0	0	2	40	3	60	4	44.44	0.43
Hepatits	5	5.43	0	0	1	20	0	0	0	0.00	0.61

Table 8: Adverse events- Others according to Regimen

Adverse events- Others	TLD (92)		ABC+L+DTG (4)		TL+ATV/r (5)		ZL+ATV/r (5)		ZL+DTG (9)		P value
	N	%	n	%	N	%	N	%	N	%	
Headache	9	9.78	0	0	3	60	0	0	1	11.11	0.10
Fatigue	10	10.87	0	0	2	40	4	80	6	66.67	0.002
Peripheral Neuropathy	0	0.00	0	0	0	0	1	20	1	11.11	<0.007
Pancreatitis	2	0.00	0	0	0	0	0	0	0	0	0.97
Myalgia	9	9.78	0	0	0	0	3	60	3	33.33	0.05
Myopathy	0	0.00	0	0	0	0	0	0	1	11.11	0.03
Alopecia	6	6.52	0	0	0	0	1	20	0	0.00	0.65

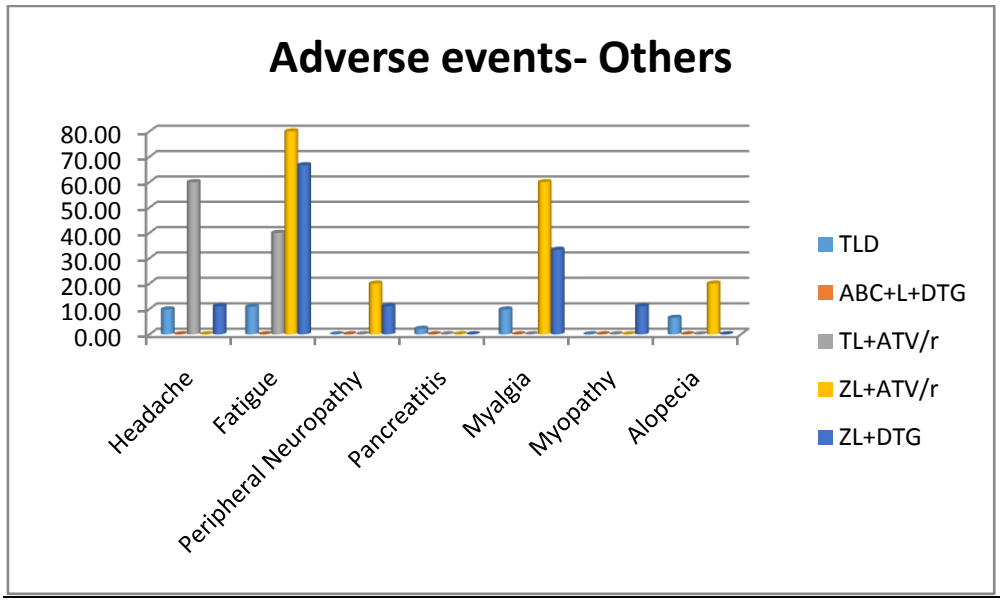

Figure 8: Adverse events- Others according to Regimen

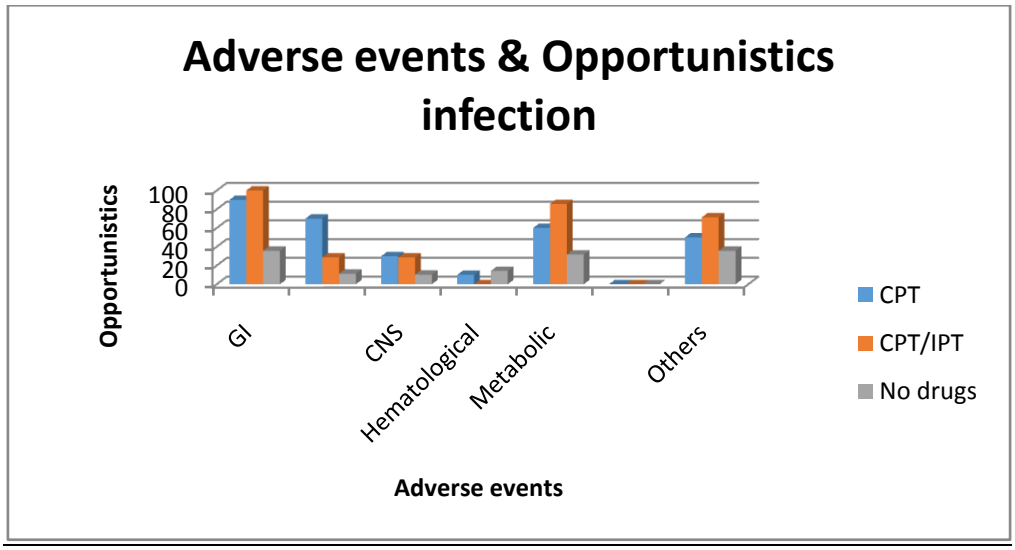

Figure 9: Adverse events according to Opportunistic infection prophylaxis

Table 9: Adverse events according to Opportunistic infection prophylaxis

Adverse Events	Opportunistic infection						P value
	CPT(10)		CPT/IPT(7)		No drugs (98)		
	N	%	N	%	N	%	
GI (51)	9	90	7	100	35	35.71	0.04
Allergic reaction (20)	7	70	2	28.57	11	11.22	0.002
CNS (15)	3	30	2	28.57	10	10.20	0.19
Hematological (15)	1	10	0	0	14	14.29	0.58
Metabolic (43)	6	60	6	85.71	31	31.63	0.14
Hyper pigmentation (0)	0	0	0	0	0	0.00	---
Others (45)	5	50	5	71.43	35	35.71	0.47

DISCUSSION

Among 115 patients enrolled for the study the largest number of patients was in the age group of 31-40 years (33.91%), followed by 21-30 years (23.48%). In the current study, out of 115 study participants, majority were female (59.13%) and male participants were 47(40.87%).

Our analysis indicated that 77.39% of participants experienced atleast one adverse event, and 30.43% individuals had more than 3 adverse events. In a study by Lili Dai et al [6], 72.2% patients had experienced more than one adverse event.

Consistent with other publications, the most frequently reported adverse reactions consisted of Gastrointestinal adverse events, seen among 51 patients (44.35%) [7, 8], followed by 43 participants (37.39%) with metabolic adverse events (44.35%). Generally, these effects cause great discomfort, and therefore can be easily perceived and reported by patients on ART.

GI adverse event nausea was experienced by participants in all the five regimen. 19.57% among the 92 patients on TLD regimen experienced nausea, followed by heartburn in 14.13%. Major GI adverse event among patients on ZL+ATV/r was diarrhea, followed by loss of appetite and nausea. Studies like Kim MJ et a [9] reported that the most common gastrointestinal side effects are diarrhea, nausea, and vomiting.

Hematologic adverse events were found to be common in patients on Zidovudine based regimen. This is consistent with other publications showing hematological side effects in AZT containing regimens, like Cristiane A et al [10] study and in Blake Max et al [11] study.

Out of 10 patients on CPT, 9 patients(90%) developed rash, and among seven patients on both CPT and IPT, all of them developed GI adverse events and six patients(85.71%) had metabolic adverse events. As reported by Moh R et al [12], in addition to placing a higher pill burden on ART treated patients, cotrimoxazole is associated with haematological toxicity and other unwanted effects such as allergic reactions, photosensitivity, interstitial nephritis. According to a study by Nanyonga SM et al [13], the prevalence of suspected IPT-linked ADRs was high, with musculoskeletal symptoms being the most frequently experienced reaction (14%), followed by dizziness (13%). However, both Cotrimoxazole and Isoniazid preventive therapy has been found to be a feasible, well tolerated and inexpensive intervention for people living with HIV to reduce HIV-related morbidity and mortality [14].

CONCLUSION

Antiretroviral therapy is becoming increasingly effective but also increasingly complex. The many adverse effects of therapy may cause symptoms affecting a variety of organ systems. Although current antiretroviral regimens are potent from an antiviral perspective, they often fail because of patient nonadherence.

To optimize adherence and hence, efficacy; clinicians must focus on preventing adverse effects, when possible, and distinguishing those that are self-limited from those that are potentially serious. As efforts continue in the development of medications with more favorable adverse effect profiles, treating physicians must remain aware of new and developing syndromes associated with antiretroviral use.

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