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PREVALENCE OF DRUG-DRUG INTERACTIONS OF ANTI-RETROVIRAL AGENTS IN HUMAN IMMUNO DEFICIENCY VIRUS POSITIVE PATIENTS

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ABSTRACT

The advent of highly active antiretroviral therapy (HAART) has decreased mortality and improved the quality of life for HIV positive people, but treatment of HIV and its associated conditions remains highly complex, With some antiretroviral agents, dozens of drugs for opportunistic illnesses (OIs), and additional therapies to manage associated conditions such as elevated blood fats, the potential for drug interactions is a pressing concern. The increasing complexity of medicine in developed societies today also carries an increased risk of interactions leading to reduced efficacy or to toxic reactions. Which anti-retrovirals should not be used with other drugs. HIV positive people need not despair if they must take a medication implicated in many interactions. Often, drug interactions can be overcome simply by raising or lowering doses however, this should never be done without the guidance of a knowledgeable practitioner. In other cases, it may be possible to replace an interacting drug with a no interacting agent that works comparably well. The problem with such lists, especially in a rapidly developing area, is that they can date quickly and should always be used with care.

KEY WORDS

Antiretroviral, Drug Drug Interactions and National AIDS control organisation.

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INTRODUCTION

Acquired Immuno Deficiency Syndrome (AIDS) is the name of the fatal illness caused by a retro virus known as Human Immunodeficiency Virus (HIV), which breaks down the body's immune system leaving the victim vulnerable to a host of life-threatening opportunistic infections, neurological disorders or unusual malignancies. The Enzyme-Linked Immuno sorbent Assay (ELISA) test was

developed to diagnose antibody to the HIV virus. Using globally accepted methodologies and updated evidence on survival to HIV with and without treatment, it is estimated that about 1.72 lakh people died of AIDS related causes in India[1,2]. Wider access to ART has resulted in a decline of the number of people dying due to AIDS related causes.

Types of treatment

Highly active antiretroviral therapy (HAART) is the cornerstone of management of patients with HIV infection. Initiation of widespread use of antiretroviral therapy marked declines in the incidence of most AIDS defining conditions and mortality both in the developed and developing world.

- Highly Active Anti-Retroviral Therapy (HAART) as a part of comprehensive HIV/AIDS care[3,6].
- Prophylaxis and treatment of Opportunistic infections in patients with HIV/AIDS.

HAART drugs do not cure HIV they only temporarily suppress viral replications and improve symptoms. Effective therapy requires the simultaneous use of three or more drugs. The need for early drug treatment should, however, be balanced against the development of toxicity. A triple drug regimen of Zidovudine (ZDV or AZT) Lamivudine (3TC) Nevirapine (NVP) as first line treatment, Which are in conformity to regional practice, the cut off CD4 count lesser than 200 cell/cubic mm will be used for initiating the treatment.

Non nucleoside Reverse Transcriptase inhibitors

- Abacavir (ABC)
- Didanisine (ddl)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- Zidovudine (ZDV or AZT)

Nucleoside Reverse Transcriptase inhibitors

- Efavirenz (EFV or EFZ)
- Nevirapine (NVP)

Protease Inhibitors

- Indinavir (IDV)
- Lopinavir/Ritonavir (LPVRTV)
- Nelfmavir(NFV)
- Ritonavir(RTV), Saquinavir(SQV)

First Line regimen for adults and adolescents

2NRTI's+ 1NNRTI

AZT + 3TC +NVP

For patient who are allergic to NVP, should be switched over to EFV

AZT + 3TC + EFV

Second Line Regimen for adults and adolescents

In case of AZT related persistent GI intolerance or severe hematological toxicity and NVP related severe hepato toxicity switch over to.

D4T + 3 TC + EFV

In case of AZT related persistent GI intolerance or severe hematological toxicity and EFV related severe hepato toxicity switch over to.

D4T + 3TC+NVP

Note: Pregnant women developing hepatotoxicity due to NVP, a switch to PIPreferably NFV or SQV is recommended.

Monitoring

When HAART initiated there should be clinical monitoring from time to time. The patient should be advised to visit clinic two weeks after initiating HAART. The clinicians then can monitor any side effects and reinforce adherence to the therapy. The patient should be advised to visit the clinic monthly for prescription refill and then once every *six* months for CD4 count. During each visit, the clinician should enquire about:

- Any new symptoms that may be related to drug toxicity
- Any symptoms of opportunistic infections
- Symptoms related to progression of HIV
- Assess the need for further counseling

Methodology

A four month hospital based prospective study was carried out at the Department of Medicine, David Johnson General Hospital, chitoor. All the necessary and relevant data were collected from in-patient case sheets, treatment charts, and laboratory charts. In addition, the patient medication history was taken and documented in a suitably designed patient data collection form. The possible DDIs (Drug-Drug Interactions) between ARVs ARVs, ARVs with

others and other with others due to concomitant use were analysed by using Stockley's Drug interactions, Micromedex online drug reference and from other relevant resources.

Inclusion criteria

- HIV positive in patients.
- HIV positive patients, already on ART
- Patients of either sex
- Patients above 18 years of age
- Patients willing to participate in the study

Exclusion criteria

- HIV positive out patients
- Patients below 18 years of age
- Pregnant HIV positive patients
- Patients not willing to participate

Source of data

- Case sheets of HIV +ve In-patients.
- Laboratory reports of HIV +ve patients.

Study materials

The following study materials were prepared and used for the study.

Informed consent form (Annexure-I)

A patient informed consent form was prepared and from the selected patients, the informed consent was obtained and enrolled in to the study, by considering study criteria.

Patient data collection form (Annexure-II)

A suitably designed patient data collection form was prepared by referring standard text books, journals, internet and other relevant resourses, which includes information of patient demographic details such as age, gender, educational, social status and also duration of disease and medication history.

Study procedure

The study was started after ethical clearance and permission from the Department of Medicine.

A prospective study was conducted by enrolling the HIV patients by considering inclusion and exclusion criteria after obtaining the written consent form the patients. The enrolled patient's medication charts were intensively monitored during their hospital stay.

All the necessary and relevant data were collected from inpatient case sheets, treatment charts, laboratory report such as demographic details of the patients, opportunistic infections, CD4 count, and route of administration with frequency. In addition, the patient's medication history was taken and documented in a suitably designed "patient Data collection Form .Possible DDIs found were classified according to a clinical significant rating, based on pharmacology, on set, and severity as described.

Classification based on severity

Major: It effects were potentially life threatening, capable of causing permanent damage, and necessitating additional treatment, hospitalization or extension of hospital stay.

Moderate: It effects were determination of a patient's clinical status, May requiring additional treatment, hospitalization or extension of hospital stay.

Minor: It affects are usually mild, having bothersome or unnoticeable consequences but not significantly affecting therapeutic out come. Additional treatment is usually not required.

Classification based on pharmacological actions:

Drug interactions are classified as pharmacokinetic and Pharmacodynamic based on pharmacological actions.

Pharmacokinetic interactions: Those in which one drug alters the rate or extent of absorption, distribution or elimination (Metabolism or Excretion) of another drug.

Pharmacodynamic interactions: Those in which one drug induces a change in a patient's response to a drug without altering the object drug's pharmacokinetics. That is one may see a change in drug action without altered plasma concentration.

Classification based on onset:

How rapidly the clinical effects of an interaction can occur determines the urgency with which preventive measures should be instituted to avoid the consequences of the interaction. Two levels of onset were used.

Rapid: The effect will be evident within 24 hours of administration of the interacting drug. Immediate action is necessary to avoid the effects the interaction.

Delayed: The effect will not be evident until the

interacting drug is admistered for a period of days or weeks. Immediate action is not required.

RESULTS

Gender distribution of the Patients

A total of 34 patients enrolled in to the study, out of which there were, 18 male and 16 female patients was shown in Table No.1.

Age distribution of the patients

Age Distribution of patients enrolled in the study. The results showed that, there were 8 (23.52 %) patients of age range between 18-30 years, 12 (35.29 %) patients of age range between 31-45 years and 14 (14.17 %) patients of age range between 46-60 years was shown in Table No.2.

Educational Status of Patients:

Educational status of patients enrolled in the study. The results showed that, 6 (17.64 %) patients had their school education, 3 (08.82 %) patients had their pre-university education, 5 (14, 70 %) patients had their university level education and 20 (58.82 %) patients were illiterate was shown in Table No.3.

Occupational status of the patients

Occupational status of patients enrolled in the study. The results showed that7 (20.58 %) patients were from agriculture, 13 (38.23 %) patients were labour 4 (11.76 %) patients were House wives, 5 (14.70 %) patients were from business, and 5 (14.70 %) patients were employees was shown in Table No.4.

Regional status of the patients

Regional status of patients enrolled in the study. The results showed that, 15 (44.11 %) patients are from urban regions and 19 (55.88 %) patients are from rural regions were shown in Table No.5.

CD4 Counts of the patients

CD4 Counts of patients enrolled in the study. The results showed that 20 (58.82 %) patients were having CD4 counts <200 and 14 (41.17 %) patients were having CD4 counts >200 [8] was shown in Table No.6.

Details of Drug Interactions of Patients in the Study

A total of 34 HIV patients were enrolled into the study, the DDIs were found in 26 (76.47 %) patients and there were no DDIs in remaining 8 (23.53 %) patients[3] were shown in Table No.7.

Number of possible DDIs

The results showed that out of 120 DDIs there were 40 (33.33 %). DDI's due to interaction between ART with other and 80 (66.66 %) DDI's due to interaction between others with others[3,5,10] was shown in Table No.8.

No of interactions per patient

Among 63 patients there were a total of 337 DDIs per patients. The results showed that , 6 (9.53 %) patients had only 1 DDI, 9(14.28 %) patients had 2 DDIs, 10(15.87 %)patients had 3DDIs, 7(11.11 %) patients had 4 DDIs , 8 (12.71 %) patients had 4DDIs, 5 (7.93 %) patients had 6 DDIs, 4(6.34 %).patients had 7 DDIs, 7 (11.11 %) patients had 8 DDIs, 2(3.18 %) patients had 9DDIs and 5(7.94 %) patients had > 10 DDIs was shown in Table.No.9.

Classification of DDIs Based on Pharmacology

The result shows that out of 120 DDIs there were 68(56.6 %) pharmacokinetic DDIs and 52(43.3 %) pharmacodynamic DDI.Among pharmacokinetic DDI 36(52 %) were due to interaction between ART with others and 32 DDI due to interaction between other drugs, and among pharmacodynamic DDI 19 DDI were due to interaction between ART with other drugs and 33 DDI were due to interaction between with other drugs[20,21] was shown in Table No.10.

Classification of DDIs based on onset

The result showed out of 120 DDIs were 44 (36.6 %) rapid drug interaction and 76 delay DDIs. Among rapid interaction 18 DDIs were due to interaction between ART with others 26 DDIs were due to interaction between other with other. And among delay interaction 40 DDIs were due to interaction between ART with others and remaining 36 DDIs were due to interaction between other drugs.

Classification of DDIs based on Severity

The results showed that out of 120 DDIs there were 30 (25 %) major DDIs. 70 (583.33 %) moderate DDIs and 20 (16.66 %) minor DDIs. Among major DDI47 (64.38 %) DDIs were due to interactions between ART with Others and 26 (35.62 %) DDIs

were due to interactions between others with others[2,3,4]. Among moderate DDIs 50 (28.90 %) DDIs were due to interactions between ART with other drugs and 123 (71.1 %) DDIs were due to interactions between other with other drugs. Among minor DDIs 69 (75.82 %) were due to interactions between ART with other drugs and 22 (24.18 %) DDIs were due to interactions between Other with Other drugs.

Analysis of interacting Drugs Based on Severity

ART with others[5,4,7]

Among the ART – other DDIs the major DDIs based on severity were due to interactions between nevirapine with fluconazole, followed by zidovudine with pyrimethamine, nevirapine with rifampin. Nevirapine with quinine, nevirapine with dexamethasone. Zidovudine with pyrazinamide nevirapine with cyclophosphamide, Efavirenz with rifampicin, Zidovudine with clarithromycin, and nevirapine with carbamazepine were identified. Among the other DDIs the moderate DDIs were due to interactions between zidovudine with acetaminophen, nevirapine with methadone, zidovudine with methadone, Efavirenz with clarithromycin, Efavirenz with methadone, zidovudine with rifampin, nevirapine with amlodipine, Efavirenz with Atorvastatin and Efavirenz with Phenytoin were identified.

Among the ART – Other DDIs were due to interactions between lamivudine with cotrimoxazole, zidovudine with fluconazole and zidovudine with Phenytoin were identified.

Others with others

DDIs the moderate DDIs were due to interactions between fluconazole with omeprazole, pyrimethamine with folic acid, iron with ofloxacin, Rifampin with omeprazole, iron with omeprazole, acetaminophen with carbamazepine flu conazole with methadone rifampin with carbamazepine, Phenytoin with omeprazole, Phenytoin with chloramphenicol, fluconazole with rifampin, rifampin with diazepam, rifampin with dexamethasone, Phenytoin with fluconazole, folic acid with Phenytoin, fluconazole with cyclosporine, rifampin with methadone, Phenytoin with cotrimoxazole, Phenytoin dexamethasone, Phenytoin with acetaminophen, and Phenytoin with rifampin were identified. Among the other – other DDIs the minor DDIs were due to interactions between isonizid with prednisolone, acetaminophen with Cholestyramine, acetaminophen with chloramphenicol and iron with Cholestyramine were identified.

DISCUSSION

Gender distribution of the patients:

Gender distribution of the patients enrolled in the study. The results showed that among 34patients, 18 were male patients and 16 were female patients. Our result is found to be similar to the studies carried out by several researches. In their study there were more no male patients when compared with female patients. The NACO reports that in the world and in India the prevalence of HIV is more in males than the females[2,3] .

Age distribution of the patients

Age Distribution of the patients enrolled in the study. The results showed that, there were more no of patients in the age range of 31-45 years 12 (35.29 %) followed by the age range of 46-60 and 18-30 years. Our findings are similar to those studies conducted by in their study there were more no of patients in the range of 30-40 years. And it differs from the studies conducted here there were more no of patients in the range of 41 to 59 years.

Regional status of the patients

Regional status of patients enrolled in the study. The results showed that, there were more no of patients were form rural 15 (44.11 %) when compared with urban 19 (55.8 %). Similar observations were made. This may be due to less awareness about AIDS in the rural area.

CD4 Counts of the patients [8,9]

CD4 Counts of patients enrolled in the study. The results showed that, there were more number of patients 20 (58.82 %) having CD4 counts <200 when compared to CD4 counts >200 14(41.17 %), which indicates the poor maintains of their disease. However, the studies reports that the CD4 count <200 is the most commonly due ay to drug

interactions. But this may be due to drug interactions and other factors.

Details of drug interactions of patients in the study

A total of 34 HIV patients were enrolled into the study, 63 patients were found having interactions, remaining 9 (12.5 %) patients were found without interactions. Among 337 of DDIs were identified of these 42.26 % (N=166) were between other drugs themselves. Our finding differed from, where DDIs are slightly higher between ARV with other drugs than other with other drugs.

Classification of DDI's based on pharmacology[10,11]

The results showed that out of 120DDI's there were more number of pharmacokinetic drug interactions 68 (56.6 %) when compared with Pharmaco-dynamic drug interactions 52(43.3 %).this could be because highly active anti-retroviral therapies are extensively metabolized by the cytochrome p450 isoenzyme system , particularly by CYP3A415.They also have the potential to interact with other drugs metabolized by CYP3A4. However, the study carried out by the reports more number of pharmacokinetics drug interactions and states that the pharmacokinetic drug interactions are most commonly associates interaction encountered in clinical practice.

Among pharmacokinetics DDIs there were more number of DDIs due to interaction between ART with others 36 (52.9 %), followed by others with others 32(47.0 %).

Among Pharmacodynamic DDIs there were more number of DDIs due to interaction between ART with others 33 (63.4 %), followed by others with others 19 (36.5 %). No DDIs were reported due to interaction between ART with ART. This may be due to standard ART combination as per the recommendations of standard treatment guidelines.

Classification of DDI's based on severity

The results showed that out of 120 DDIs there were more number of moderate drug interactions, 7 (58.33 %) followed by minor drug interaction 20 (16.66 %)and major drug interaction 30(25.0 %). Among moderate DDIs there were more number of DDIs due to interactions others with others 50(71.42 %), followed by ART with others 20 (28.57 %).

Among minor DDIs there were more number of DDIs due to interactions others with others 7 (35.0 %), followed by ART with others 13(65.0 %). Among minor DDIs there were more number of DDIs due to interactions others with others 19 (63.3 %), followed by ART with others 11(36.6 %).

Classification of DDI's based on onset

The results showed that out of 120 DDIs there were more number delayed DDIs 76(63.3 %) when compared to rapid DDIs 44(36.6 %)[7,8]. Among delayed DDIs there were more number of DDIs due to interactions between others with others 36(47.36 %), followed by ART with others 40(52.63 %).

Among rapid DDIs there were more number of DDIs due to interactions between ART with other (40.9 %), followed by others with others 26 (59.09 %).

Table No.1: Gender distribution of the patients

S.No	Gender distribution	Total no of patients n=34	% of total no of patients
1	Male	18	57.94 %
2	Females	16	47.25 %

Table No.2: Age Distribution of the patients

S.No	Age	Gender		Total no of Patients n=34	% of total no of patients
		Male	Female		
1	18-30	4	4	8	23.52 %
2	31-45	8	6	12	35.29 %
3	46-60	9	5	14	41.17 %

Table No.3: Educational status of patients

S.No	Educational status	Gender		Total no of Patients n=34	% of total no of patients
		Male	Female		
1	School	2	4	6	17.64 %
2	Pre- University	2	1	3	8.82 %
3	University	3	2	5	14.70 %
4	Illiterate	13	7	20	58.82 %

Table No.4: Occupational status of patients

S.No	Occupational status	Gender		Total no of Patients n=34	% of total no of patients
		Male	Female		
1	Agriculture	6	1	7	2058 %
2	Labour	8	5	13	38.23 %
3	House wife's	0	4	4	11.76 %
4	Business	5	0	5	14.70 %
5	Employee	4	1	5	14.70 %

Table No.5: Regional status of patients

S.No	Regional status	Gender		Total no of Patients n=34	% of total no of patients
		Male	Female		
1	Urban	10	5	15	44.11 %
2	Rural	9	10	19	55.88 %

Table No.6: CD4 Counts of the patients

S.No	CD4 Cells	Total no of patients n=34	% of total no of patients
1	<200 CD4 Cells	20	58.82 %
2	>200 CD4 Cells	14	41.17 %

Table No.7: Details of Drug Interactions of patients in the study

S.No	Total no of patients enrolled in study	Total patients had interaction in the study	Total patients without interactions in the study
1	34 (100 %)	26 (76.47 %)	8 (23.53 %)

Table No.8: Number of possible DDIs

S.No	Drug Interactions	Total no of interactions n=120	% of total no of interactions
1	ART-OTHER	40	33.33 %
2	OTHER-OTHER	80	66.66 %

Table No.9: No of interactions per patient

S.No	No. of Interactions	Total no of patients n=34	% of total no of patients
1	1.Interactions	4	**11.7 %**
2	2.Interactions	3	**8.8 %**
3	3.Interactions	5	**14.7 %**
4	4.Interactions	**6**	**17.64 %**
5	5.Interactions	8	**23.52 %**
6	6.Interactions	9	**26.47 %**
7	**Average**	**5.66**	**---**

Table No.10: Clasification of DDIs based on pharmacology

S.No	Types of drug- drug interaction	Drug Interaction		Total no of interaction	% of total no of drug-drug interaction
		ART- other	Other-Other		
1	Pharmacokinetic	36 (52.9%)	32 (47.0%)	68	56.6 %
2	Pharmacodynamic	19 (36.5%)	33 (63.4%)	52	43.3 %

Table No.11: Classification of DDIs based on onset

S.No	Types of drug – drug interaction	Drug interactions		Total no of drug interactions	% of total no of drug interactions
		ART with others	Other-other		
1	Rapid	18 (40.9 %)	26 (59.9 %)	44	36.6 %
2	Delay	40 (52.63 %)	36 (47.36 %)	76	63.3 %

Table No.12: Classification of DDIs based on Severity

S.No	Types of drug interactions	Drug interactions			Total no of drug interactions n=120	% of total no of drug interactions
		Art-Art	ART-Other	Other-Other		
1	Major	-	19 (63.3 %)	11 (36.6 %)	30	25 %
2	Moderate	-	20 (28.57 %)	50 (71.42 %)	70	58.33 %
3	Minor	-	13 (65.0 %)	7 (35.0 %)	20	16.66 %

Table No.13: Analysis of Interacting drugs based on severity

Drug Class	Drug	Interacting Drug	No of Interactions	Remarks
Major Drug Interactions				
ART-ART	**-**	**-**	**-**	**-**
ART – Other Drugs	Zidovudine	Pyrazinamide	3	Concurrent use of Pyrazinamide and zidovudine may result in decreased efficacy of Pyrazinamide.
	Zidovudine	Pyrimethamine	8	Concurrent use of pyrimethamine and Zidovudine may result in an increased risk of bone marrow suppression
	Zidovudine	Clarithromycin	2	Concurrent use of clarithromycin and zidovudine may result in decreased zidovudine concentrations
	Nevirapine	Quinine	4	Concurrent use of nevirapine and quinine may result in decreased quinine efficacy.
	Nevirapine	Rifampin	6	Concurrent use of nevirapine and rifampin may result in decreased nevirapine serum concentrations and possible loss of nevirapine efficacy.
	Efavirenz	Rifampin	3	Concurrent use of Efavirenz and rifampin may result in decreased serum Efavirenz concentrations.
Total			26	
OTHER-OTHER DRUGS	Fluconazole	Cotrimoxazole	10	Concurrent use of cotrimoxazole and fluconazole may result in an increased risk of cardio toxicity (qt prolongation, torsades de points, cardiac arrest).

	Fluconazole	Alprazolam	1	Concurrent use of alprazolam and fluconazole may result in increased alprazolam concentrations and potential alprazolam toxicity (excessive sedation and prolonged hypnotic effects).
	Cotrimoxazole	Methotrexate	4	Concurrent use of methotrexate and pantoprazole may result in increased concentration of methotrexate and its metabolite and an increased risk of methotrexate toxicity.
	Ondansetron	Ofloxacin	4	Concurrent use of ofloxacin and ondansetron may result in increased risk of qt interval prolongation.
Total			19	
Moderate Drug Interactions				
ART-ART	-	-	-	-
	Nevirapine	Amlodipine	3	Concurrent use of amlodipine and nevirapine may result in reduced amlodipine efficacy.
	Nevirapine	Methadone	8	Concurrent use of methadone and nevirapine may result in an increased risk of Opioid withdrawal symptoms (insomnia, pain, nausea, sweating, and anxiety).
	Zidovudine	Methadone	6	Concurrent use of methadone and zidovudine amy result in an increased risk of zidovudine toxicity (lethargy, fatigue, and anaemia).
	Efavirenz	Methadone	4	Concurrent use of Efavirenz and methadone may result in an increased risk of Opioid withdrawal symptoms (insomnia, pain, nausea, sweating, anxiety)
	Efavirenz	Atorvastatin	3	Concurrent use of Atorvastatin and Efavirenz may result in decreased Atorvastatin plasma concentrations.
	Efavirenz	Phenytoin	3	Concurrent use of Efavirenz and Phenytoin may result in decreased Efavirenz and/or Phenytoin plasma concentrations.
Total			27	
OTHER-OTHER DRUGS	Phenytoin	Cotrimoxazole	2	Concurrent use of Phenytoin and cotrimoxazole may result in an increased risk of Phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremors).
	Phenytoin	Acetaminophen	2	Concurrent use of acetaminophen and Phenytoin may result in decreased acetaminophen effectiveness and an increased risk of hepatotoxicity.
	Phenytoin	Omeprazole	5	Concurrent use of omeprazole and Phenytoin may result in an increased risk of Phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)
	Phenytoin	Chloramphenicol	5	Concurrent use of Phenytoin and chloramphenicol may result in an increased risk of Phenytoin toxicity (ataxia, hyperreflexia, nystagmus, and tremor).
	Fluconazole	Rifampin	5	Concurrent use of fluconazole and rifampin may result in decreased fluconazole serum concentrations and antifungal activity.
	Fluconazole	Cyclosporine	3	Concurrent use of fluconazole and cyclosporine may result in an increased risk of cyclosporine toxicity (renal dysfunction, cholestasis, paresthesias)
	Rifampin	Dexamethasone	4	Concurrent use of dexamethasone and rifampin may result in decreased dexamethasone effectiveness
	Rifampin	Methadone	3	Concurrent use of methadone and rifampin may result in decreased serum methadone levels and the appearance of withdrawal symptoms.
	Rifampin	Diazepam	5	Concurrent use of diazepam and rifampin may result in decreased diazepam effectiveness.

	Pyrimethamine	Folic Acid	12	Concurrent use of folic acid and pyrimethamine may result in loss of pyrimethamine efficacy.
	Iron	Omeprazole	8	Concurrent use of iron and omeprazole may result in reduced non-heme iron bioavailability.
TOTAL			54	
Minor Drug Interactions				
ART-ART	-	-	-	-
ART-OTHER DRUGS	Lamivudine	Cotrimoxazole	31	Concurrent use of cotrimoxazole and lamivudine may result in an increased risk of lamivudine adverse effects.
	Zidovudine	Cotrimoxazole	18	Concurrent use of ctrimozole and zidovudine Amy result in increased serum concentrations of zidovudine.
	Zidovudine	Fluconazole	18	Concurrent use of fluconazole and zidovudine may result in increased zidovudine concentrations.
Total			67	
OTHER-OTHER DRUGS	Isoniazid	Prednisolone	6	Concurrent use of isoniazid and prednisone may result in decreased isoniazid effectiveness
	Iron	Cholestyramine	2	Concurrent use of Cholestyramine and iron may result in decreased iron effectiveness.
	Acetaminophen	Cholestyramine	6	Concurrent use of Cholestyramine and acetaminophen may result in decreased acetaminophen effectiveness
	Acetaminophen	Chloramphenicol	6	Concurrent use of acetaminophen and chloramphenicol may result in chloramphenicol toxicity (vomiting, hypotension, hypothermia).
	Omeprazole	Diazepam	2	Concurrent use of omeprazole and diazepam may result in enhanced and prolonged diazepam effects.
Total			28	

CONCLUSION

The study revealed that there was more number of DDIs study site .with an average of 5.34 % DDIs per patients. And the severity of the DDIs indicates that there were also a substantial number of moderate DDIs173 (51.33 %) and also a substantial number of major interactions 73 (21.66 %). The majority of DDIs were due to interaction between others with others 171(51 %) followed by ART with others 166(49 %) and there were no DDIs between ART with ART. These interactions may lead to therapeutic failure and also increase hospital admission and cost of therapy. The wast number of medication are available for the prescriber it is essential to update their knowledge about DDI and also there is a need to conduct the educational programs for minimizing them. Majority of DDIs were available by dose adjustment & avoiding concomitant administration[12]. This can be achieved by strengthening the pharmacovigilence set up at study site.

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