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Original Research Article

A study of cutaneous adverse drug reactions among HIV infected adults in a tertiary care centre in north Karnataka

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ABSTRACT

Background: CADRs are known to be more common in HIV with severity ranging from mild to life threatening ones.
Aims:a). To know the epidemiology and clinical profile of mucocutaneous manifestations of ADRs among HIV patients. b). To correlate the spectrum of mucocutaneous manifestations with laboratory derangements.
Materials and Methods : Adult HIV patients with suspected CADRs were recruited. History about epidemiological data, culprit drug and spectrum of mucocutaneous manifestations were taken. Severity scoring was done according to modified Hartwig and Siegels system and causality assessment was done using Naranjo system. Investigations like CBC, RFT, LFT, RBS, serum electrolytes, urine examinations were carried out.
Results: Out of 110 patients, male to female ratio was 0.83:1. Most common age group was 31-40 years. Most common presentation was maculopapular eruption (39.09%) followed by FDE (11.8%), angioedema (10.9%), DRESS (10%), SJS(7.27%) and others. Most common offending drug group was ART (40.9%) followed by antibiotics (20.9%). Most common laboratory derangement was increase in liver enzymes (SGOT in 24.5%, SGPT in 21.8%) followed by eosinophilia (19.1%), raised bilirubin and serum creatinine (5.5%). There was a significant association between raised liver enzymes, total bilirubin, Eosinophilia and raised Serum creatinine with DRESS and also significant association between raised liver enzymes and raised Serum creatinine with SJS.
Conclusion: Prompt diagnosis, isolation of the offending drug and treatment of the CADRs are warranted, since severe reactions may be associated with internal organ damage.

1. Introduction

With an increase in the number of drugs, adverse drug reactions have become very common in recent times. Among them cutaneous reactions have been steadily gaining importance and constitute a major proportion of all the adverse drug reactions. Innumerable epidemiological and clinical studies have highlighted the various aspects of this disorder. A large amount of data on cutaneous adverse drug reactions is being constantly updated. The early detection and treatment of cutaneous adverse drug reactions and identification of the causative agent are essential to prevent the progression of the reaction and preventing additional exposures. [1]

The severity of such reactions ranges from mild to severe ones. Poly pharmacy can lead to drug interactions and thereby increase the rate of ADRs. [1] Iatrogenic factors that lead to adverse drug reactions include inappropriate dosage, immune dysregulation and altered metabolism in HIV patients, [2,3] inappropriate combinations of drugs and use of drugs not recommended for a particular age group.

Skin diseases including adverse reactions to drugs are thought to be more common among patients with human immunodeficiency virus infection than among

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other persons.[4] Though the introduction of highly active antiretroviral therapy has led to significant reduction in AIDS related morbidity and mortality, the side effects and drug reactions due to such drugs are increasing. The causative drug in such adverse reactions need not be always ART, other drugs used in such individuals like ATT, drugs used to treat opportunistic infections or self medications can also cause reactions. The severity of such reactions ranges from mild to severe ones.[5]

Different types of CADRs are morbilliform eruptions, fixed drug eruptions, phototoxicity, urticaria, exfoliative dermatitis, erythema multiforme, DRESS, Steven Johnson syndrome and toxic epidermal necrolysis. These reactions are commonly accompanied with derangement in laboratory parameters which may alter the course of the illness.

There are many studies regarding CADRs in HIV individuals due to ART but scanty for other drugs in general. So, this study was conducted to know the epidemiology, clinical pattern, associated laboratory parameter derangements in cutaneous adverse drug reactions in HIV individuals in our set up.

2. Materials and Methods

This observational study was conducted in a tertiary care centre after obtaining institutional ethical committee clearance. Total numbers of patients included was 110. All adult HIV patients with suspected cutaneous adverse reaction to any drug attending Belagavi Institute of Medical Sciences, Belagavi India were recruited after obtaining informed written consent. Detailed history regarding epidemiological data, HIV status, offending drug and any significant past history were elicited. Systemic examination and mucocutaneous examination was done in detail and the pattern of CADR was noted. Severity of the cutaneous adverse drug reaction was graded according to modified Hartwig and Siegels scoring system as mild, moderate and severe reaction.[6]Causality assessment was done using Naranjo causality scale as definite, probable or possible.[7] Necessary investigations like CBC, RFT, LFT, RBS, peripheral smear, serum electrolytes, urine examinations were carried out. The results obtained were studied using statistical analytic methods.

3. Results

3.1. Statistical analysis

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and SD.

3.2. Graphical representation of data

MS Excel and MS word was used to obtain various types of graphs such as bar diagram and Pie diagram.

p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

3.3. Statistical software

MS Excel**,** SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

Total no of patients included in the study was 110. Age distribution of the patients is shown in Table 1. Most common age group affected was 31 to 40 years (40.9%). Out of 110 patients, 54.5% were females and 45.5% were males (M: F=0.8:1) and 86.4% were married and 13.6% were unmarried.

Occupation distribution of patients in the study is as follows. Most of the patients were labourers (28.18%) followed by farmers (25.45%) and other occupation. Majority of the patients belonged to lower middle socioeconomic status (47.3%) followed by upper lower class (27.3%), upper middle class (19.1%) and lower class (6.4%) according to modified Kuppuswamy classification.

Among females, mean CD4 count was 379.38 $\pm$ 246.84 cells/mm^3 and among males 332.32 $\pm$ 261.17 cells/mm^3. There was no significant association between gender and CD4 count (Table 2).

Majority of the patients presented with maculopapular eruption (39.09%) (Figures 1, 2 and 3) followed by FDE (11.8%) (Figures 4 and 5), angioedema (10.9%), DRESS (10%) (Figure 6), SJS (7.27%), urticaria (6.4%), pruritis (6.4%), EM (4.5%) (Figure 7), acneiform eruption (3.6%) (Figure 8), photoallergic reaction (2.72%), papular eruption (1.8%), vasculitis (1.8%) (Figure 9) and TEN (0.9%) (Figure 10). Of the 110 patients, 18 patients had >1 cutaneous presentation (Table 3).

Out of 110 cases, 40.9% of the CADRs were due to ART, 20.9% due to antibiotics, 8.2% due to NSAIDs, 2.7% due to antiepileptics, 1.8% due to ATT, 0.9% due to Herbal medicines and 24.5% due to unknown drugs (Table 4).

The most common route of administration of the culprit drug was oral (95.5%) followed by intramuscular route (3.6%). According to Naranjo scoring system, 57.27% patients had probable causality, 40% had possible causality and 2.72% had definite causality. Majority of the patients (72.7%) had mild reaction, followed by moderate (25.5%) and severe reaction (1.8%) according to modified Hartwig and Siegels system.

Most common laboratory derangement seen was increase in liver enzymes (SGOT increased in 24.5%, SGPT increased in 21.8%) followed by eosinophilia (19.1%), increased bilirubin and serum creatinine (5.5% each) (Table 5).

Mean CD4 count and cutaneous ADR is shown in Table 6.

Among SJS patients, 62.5% had increased liver enzymes, 12.5% had increased ALP, bilirubin, eosinophils, TLC, ESR and 37.5% had increased serum creatinine which shows there was a significant association between increased liver enzymes and raised Serum creatinine with SJS (Table 7).

Among patients with DRESS, SGOT was raised in 100%, SGPT raised in 81.8%, total bilirubin raised in 36.4%, eosinophilia in 90.9% and raised serum creatinine in 18.2%. This shows that there was a significant association between increased liver enzymes, total bilirubin, Eosinophilia and raised serum creatinine with DRESS (Table 8).

We had a single case of TEN with raised liver enzymes, serum creatinine and serum potassium levels with low sodium.

There was no significant association between deranged laboratory parameters with maculopapular eruption, EM, urticaria, angioedema, FDE, acneiform eruption, pruritis, vasculitis, lichenoid and photosensitive drug rash.

Table 1: Age distribution of patients

Age	No of patients	%
18-20 years	7	6.4%
21 to 30 years	18	16.4%
31 to 40 years	45	40.9%
41 to 50 years	23	20.9%
51 to 60 years	15	13.6%
>60 years	2	1.8%
Total	110	100.0%

Table 2: CD4 count and Sex distribution

Sex	CD4 Count			P value
	Mean	SD	Median	
Female	379.38	246.84	331.50	0.338
Male	332.32	261.17	299.50	

4. Discussion

Adverse drug reactions forms an important and common problem in both inpatient and outpatient setting. Occurrence of these ADRs is one of the commonest causes for poor adherence to treatment. Knowledge of these drug eruptions, the causative agents and the prognostic indicators are essential for the clinician for better management of these cases and to avoid them for future use.

Females outnumbered males in our study with male to female ratio of 0.83:1. This is in accordance with the study done by Emmanuel et al[8] but not with a study done by Anshu Kumar Jha.[9] Most of the studies reported in the literature show a higher number of females as seen in our study. Although not entirely clear, these differences

Table 3: Cutaneous adverse drug reactions (CADRs) among patients

Clinical presentation	No of patients	%
Maculopapular eruption	43	39.09%
FDE	13	11.8%
Angioedema	12	10.9%
DRESS	11	10.0%
SJS	8	7.27%
Urticaria	7	6.4%
Pruritis	7	6.4%
EM	5	4.5%
Acneiform eruption	4	3.6%
Lichenoid eruption	3	2.7%
Photo allergic reaction	3	2.72%
Vasculitis	2	1.8%
Papular eruption	2	1.8%
TEN	1	0.9%

Table 4: Causative drug group distribution among patients

Drug Group	No of patients	%
Antibiotics	23	20.9%
ART	45	40.9%
NSAIDS	9	8.2%
Antiepileptic	3	2.7%
ATT	2	1.8%
Herbal medication	1	0.9%
Unknown	27	24.5%
Total	110	100.0%

Table 5: Deranged laboratory parameters among patients

Deranged laboratory parameters	Total patients	Percentage
SGOT increased	27	24.5%
SGPT increased	24	21.8%
ALP increased	6	5.5%
Low Protein	8	7.3%
Total bilirubin increased	6	5.5%
Eosinophilia	21	19.1%
TLC increased	6	5.5%
Hb decreased	16	14.5%
ESR increased	3	2.7%
HbS Ag positivity	1	0.9%
Serum Electrolytes abnormality (Na+low ,K+ high)	1	0.9%
Urine abnormality	3	2.7%
Serum creatinine raised	6	5.5%

Table 6: Mean CD4 count and cutaneous ADRs.

Cutaneous ADRs	Mean CD4 count(cells/mm^3)
Maculopapular rash	422.66
TEN	369
EM	453
Acneiform eruption	253
SJS	331.87
Lichenoid eruption	570.33
DRESS	297.09
Angioedema	422.72
Urticaria	381.85
Papular eruption	361.5
Vasculitis	563.5
FDE	271.30
Photoallergic reaction	293

Table 7: Deranged laboratory parameters in SJS

Deranged laboratory parameters	SJS				P value
	Yes		No		
	No of patients	%	No of patients	%	
SGOT increased	5	62.5%	22	21.8%	0.024*
SGPT increased	5	62.5%	19	18.8%	0.011*
ALP increased	1	12.5%	5	5.0%	0.435
Protein Low	0	0.0%	8	7.9%	0.381
Total bilirubin increased	1	12.5%	5	5.0%	0.435
Eosinophilia	1	12.5%	20	19.8%	0.525
TLC increased	1	12.5%	5	5.0%	0.435
Hb decreased	2	25%	14	13.9%	0.495
ESR increased	1	12.5%	2	2.0%	0.107
Serum Electrolytes abnormality	0	0.0%	1	1.0%	0.764
Urine abnormality	0	0.0%	3	3.0%	0.600
Serum Creatinine increased	3	37.5%	3	3.0%	<0.001*

*P value <0.05 and is considered statistically significant

Table 8: Deranged laboratory parameters in DRESS

Deranged laboratory parameters	DRESS				P value
	Yes		No		
	No of patients	%	No of patients	%	
SGOT increased	11	100.0%	16	16.2%	<0.001*
SGPT increased	9	81.8%	15	15.2%	<0.001*
ALP increased	1	9.1%	5	5.1%	0.576
Low Proteins	0	0.0%	8	8.1%	0.328
Total bilirubin increased	4	36.4%	2	2.0%	<0.001*
Eosinophilia	10	90.9%	11	11.1%	<0.001*
TLC increased	1	9.1%	5	5.1%	0.576
Hb decreased	2	18.2%	14	14.1%	0.718
ESR increased	2	18.2%	1	1.0%	0.001*
Serum Electrolytes	0	0.0%	1	1.0%	0.738
Urine abnormality	0	0.0%	3	3.0%	0.558
Serum creatinine raised	2	18.2%	4	4.0%	0.05*

*P value <0.05 and is considered statistically significant

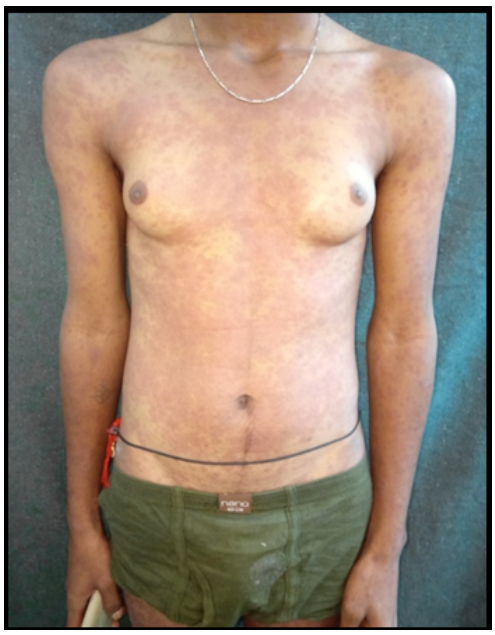

Fig. 1: Nevirapine induced maculopapular rash

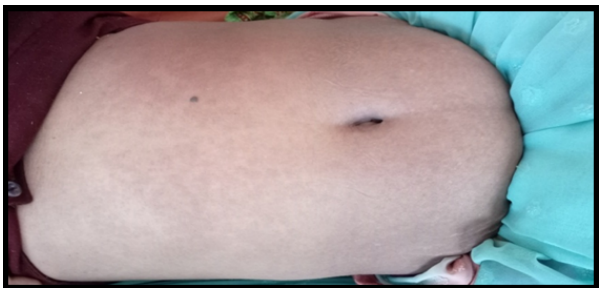

Fig. 2: Maculopapular rash due to Efavirenz

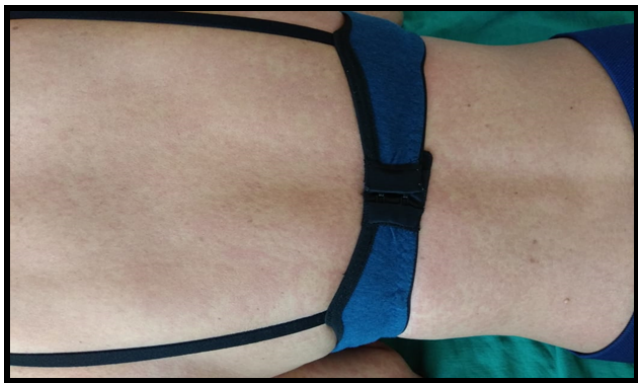

Fig. 3: Maculopapular rash due to Efavirenz

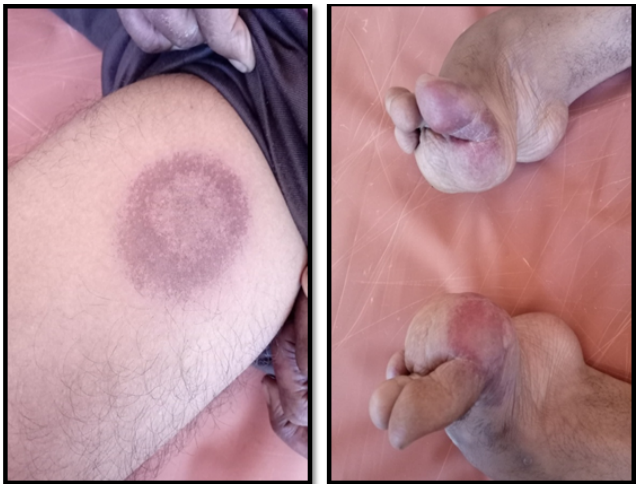

Fig. 4: Fixed drug eruption due to Ofloxacin

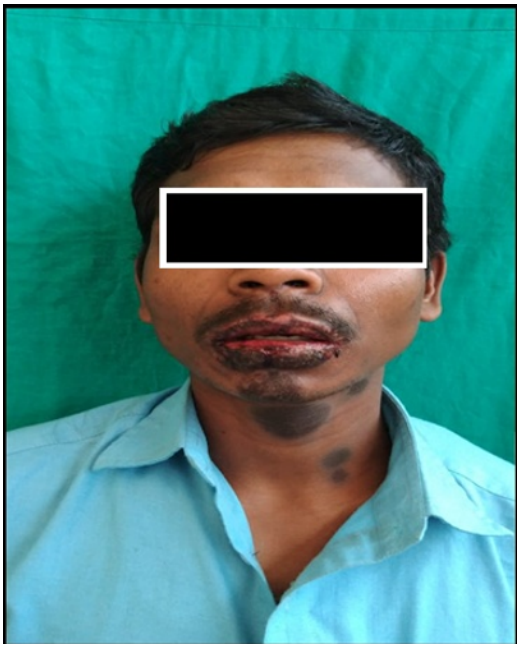

Fig. 5: Fixed drug eruption with oral involvement due to Metronidazole

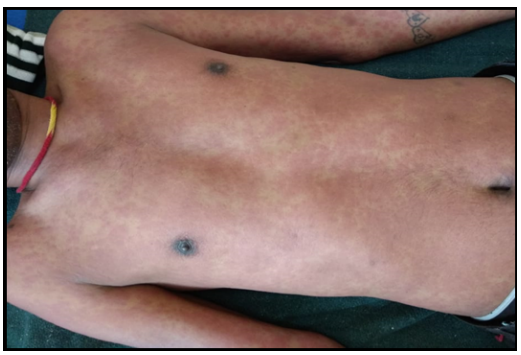

Fig. 6: DRESS due to Phenobarbitone

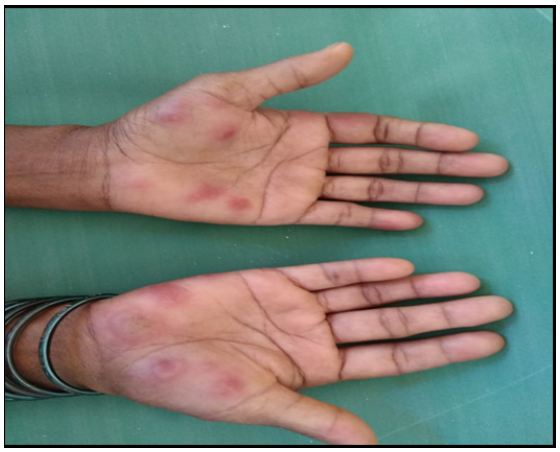

Fig. 7: erythema multiforme due to Cotrimoxazole

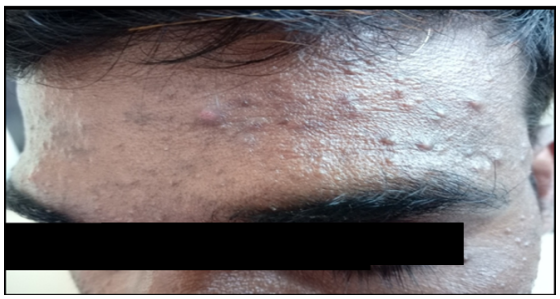

Fig. 8: Acneiform eruptions due to ATT drugs

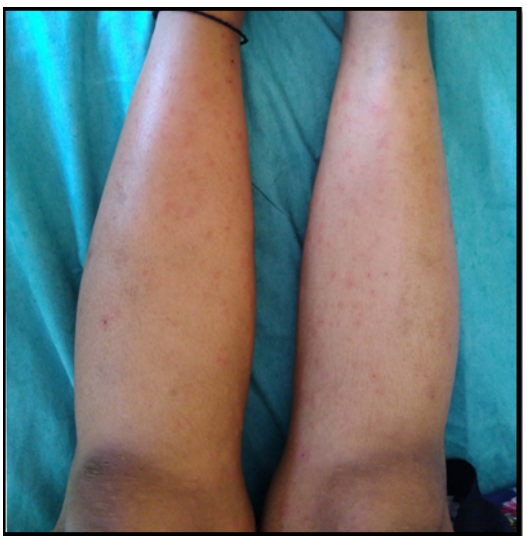

Fig. 9: vasculitis due to an unknown drug

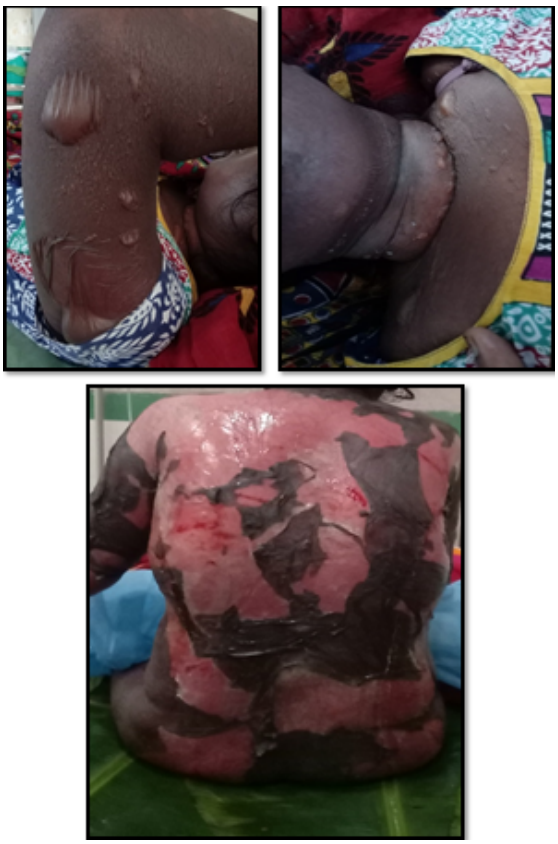

Fig. 10: Nevirapine induced TEN

have been attributed to gender related differences in pharmacokinetic, immunological and hormonal factors.[10]

Majority of the patients were middle aged (31 to 40 years). Youngest patient was 18years old and oldest patient was 67 years old. This finding is in accordance with the study done by Padukadan et al[11] and Emmanuel et al where in the mean age group was 41+/- 11.36 years.[8] This could be because of the fact that HIV is more prevalent in the adult population.

The most common CADR was maculopapular eruption followed by FDE. This is in concordance with studies done by SA Coopman et al and Gail Todd et al[12,13] where in the most common presentation was maculopapular rash followed by EM and urticaria in HIV patients.[12]

The common presentation of CADRs was also maculopapular rash followed by urticaria and FDE in general population as seen in studies done by Thakkar et al and Modi et al[14,15] where as it was angioedema and urticaria followed by maculopapular rash in a study done by Akpinar et al.[16]

The most common drug implicated was ART followed by antibiotics in our study, this could be because of the fact that patients tend to consult the physician soon after an ADR to ART as they have to take these medications lifelong. Patients tend to stop other drugs which are given for milder

ailments on their own and less likely to seek medical help. This is in accordance with the study done by Mayur Popat Pawar et al where in the most common drug implicated was antiretroviral drugs (75.56%) followed by antimicrobials, antiepileptics and NSAIDs.[17]

In our study majority had a probable causality followed by possible causality and definite causality according to Naranjo scoring system which is in concordance with a study done by Anshu Kumar Jha et al where in they had a probable causality of 66.04% and a possible causality of 33.96%.[9] This causality association is done in order to determine whether drug discontinuation is mandatory, as well as to put emphasis on patient education in order to avoid the development of ADRs in the future.

In our study, majority of the patients had mild followed by moderate and severe drug reaction. It is in accordance with other studies.[18,19]

The most common laboratory derangement was increase in liver enzyme levels followed by eosinophilia, increased bilirubin and raised serum creatinine. This finding is in accordance with the study done by Colafigli et al, where increased liver enzymes were seen in 22.3%.[20] Liver is known to be affected in various ADRs as the drug metabolism tends to occur here. Some drugs are directly injurious and others are transformed by the liver into chemicals that can cause injury. There are three types of liver toxicity; dose dependent toxicity, idiosyncratic toxicity and drug allergy. Renal is also affected in ADRs as this is the main route of drug excretion.

There was significant association between raised liver enzymes and raised serum creatinine with SJS in our study. In a study done by Aroni Chatterjee el al, where in they studied SJS patients with HIV, they found that there was increase in mean BUN and serum creatinine in 67% and raised liver enzymes in 38%.[21]

We had only one patient with TEN to Nevirapine. She had raised liver enzymes, raised serum creatinine and BUN, low Na+ and high K+ levels. In a study done by Aroni Chatterjee el al, where in they studied TEN patients with HIV, they found that there was increase in mean BUN and serum creatinine in 54% and liver enzymes raised in 47%.[21]

There was significant association between increased liver enzymes, total bilirubin, Eosinophilia and raised Serum creatinine with DRESS. Liver is one of the commonly involved internal organs in DRESS, as there will be detoxification defect leading to reactive metabolite formation and immunological reaction. Eosinophilia is also common because inflammatory cascade may be induced by interleukin 5 release from drug specific T cells.

We didn't find any significant association between deranged laboratory parameters and Maculopapular eruption, EM, urticaria, angioedema, FDE, Acneiform, Pruritis, Vasculitis, lichenoid, or photosensitive drug rash.

5. Conclusion

Though the global mortality from HIV has significantly declined due to highly active antiretroviral therapy, there has been a concurrent increase in the incidence of cutaneous drug reactions. With increasing recognition of variety of clinical manifestations of CADRs with anti-retroviral and other drugs, elucidation of underlying cellular and molecular mechanisms and identification of high risk people are needed. Timely identification of these ADRs, stopping of the offending drug and prompt treatment at the earliest is advised as these severe cutaneous ADRs are associated with internal organ damage.

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7. Conflict of Interest

The authors declare they have no conflict of interest.

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