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Original Research Article

A Study on Pattern of Dermatological Adverse Drug Reactions Due to Anti-Retroviral Therapy in HIV Infected Patients in Tertiary Care Teaching Hospitals in North India

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Conflict of interest: Nil

Abstract:

Aim & Objective: To study pattern of dermatological ADRs due to anti-retroviral therapy in HIV infected patients in tertiary care teaching hospitals in North India.

Material & Methods: A prospective observational study was conducted over a period of 15 months at Anti-retroviral therapy centre under department of internal medicine, G.S.V.M Medical College, Kanpur in association with department of pharmacology of tertiary care teaching hospitals in Uttar Pradesh, India. All HIV positive patients, previously registered and new; attending O.P.D. who encountered ADRs were enrolled in our study irrespective to their age and sex. Data was collected using ADR reporting form issued by Indian Pharmacopoeia Commission. Causality assessment was done by using Naranjo's Probability Scale. Modified Hartwig severity scale was used to evaluate severity, WHO criteria for seriousness and guidelines of council for international organizations of medical sciences to decide the predictability of ADRs.

Results: A total no of 250 patients encountered various types of ADRs during the study period. Total number of ADRs recorded was 452. Out of total ADRs (n=452) recorded, 10.8% (n=49) were dermatological ADRs. Most common dermatological ADR was skin rash. Most of dermatological ADRs were of mild type and probable in nature on causality assessment.

Conclusion: Female gender, baseline CD4 absolute count above 250 cells/mm3, were predictors for nevirapine-associated rash in HIV patients. We suggest that more stringent evaluation and monitoring should be carefully done in all HIV/AIDS patients who will receive and on NVP therapy, especially if they have the above predictors.

Keywords: Dermatological ADRs, HIV, Anti-retroviral Therapy, Skin Rash & CD4 count.

Introduction

The design of pre-marketing clinical trials precludes the representation of important subpopulations such as children, the elderly persons and people with co-morbidities. Therefore, post-marketing surveillance activities are required to monitor the safety profile of drugs in real clinical practice.

Furthermore, individual variation in pharmacogenetic profile, the immune system, drug metabolic pathways and drug-drug interactions, study population, sample size, race and other study factors affect the pattern of adverse effects seen with different studies. Thus, the safety of a drug is a major clinical consideration before and after it is marketed.[1] All drugs carry the potential for causing injury through adverse drug reactions even if used appropriately. Adverse drug reactions (ADRs) are an important cause of morbidity and mortality in hospital settings [2]. Among them dermatological reactions have been steadily gaining importance and constitute a major proportion of all the adverse drug reactions.

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. Most often adverse drug reactions go unnoticed or are not reported. There is lack of awareness and inadequate training about drug safety monitoring procedures among

healthcare professionals in India. Anti-Retroviral therapy induced ADRs may significantly impact patient's quality of life. Increase in use of antiretroviral drugs increases the risk for ADRs, resulting in humanistic and economic burden to the HIV infected patients as well as to the society.

Dermatological ADRs are an important concern for a healthcare practitioner. Comprehensive, factual knowledge regarding pattern, severity and causative agents generated from a prospective study can help physicians in choosing safer drugs and therefore can be helpful to society at large.

Myriads of dermatological toxicities are associated with antiretroviral drugs like hypersensitivity reactions, urticaria, morbilliform eruptions, SJS/TEN syndrome, photoallergic reactions, skin and nail pigmentation etc.[3]

There is paucity of data regarding the safety profile of HIV/AIDS chemotherapy in Northern India. So the objective of the current study was to analyse the pattern of dermatological adverse drug reactions in HIV infected patients treated with antiretroviral therapy in tertiary care teaching hospitals.

This systematic study at Anti-retroviral therapy centre G.S.V.M. medical college, Kanpur in association with department of pharmacology of tertiary care teaching hospitals in Uttar Pradesh, India; concerning dermatological adverse drug reactions pertaining to anti-retroviral therapy in HIV positive patients will help physicians to gain a working knowledge of these adverse effects and would be beneficial to the HIV infected patients, with the ultimate goal of improving the prescription habits and improving the tolerability and effectiveness of HIV treatment by promoting the early recognition of potentially serious adverse effects.

Therefore, keeping in mind the above objective this study was conducted to assess the pattern of dermatological ADRs in HIV infected patients receiving anti-retroviral therapy.

Material & Methods

A prospective observational study was conducted over a period of 15 months at Anti-retroviral therapy centre under department of internal medicine, G.S.V.M Medical college, Kanpur in association with department of pharmacology of tertiary care teaching hospitals in Uttar Pradesh, India.

Inclusion criteria

1. Both newly and previously registered HIV positive patients who were on anti-retroviral therapy and experienced ADRs.

2. Patients of both gender

3. Patients who gave written informed consent.

Exclusion criteria

1. Patients unable to respond to verbal questions.

2. Pregnant/ lactating females.

3. Patients with concomitant disorders such as diabetes mellitus and hypertension.

Before enrolling the patients into the study, written informed consent was obtained. After enrolment baseline laboratory investigations such as haemoglobin estimation, total leukocyte count, differential leukocyte count, serum creatinine, blood urea, serum bilirubin, SGOT, SGPT, blood sugar, CD4 count etc. were done. ADR monitoring was done in a systematic manner adopting both spontaneous and intensive monitoring approaches. Adverse drug reaction reporting form provided by Indian Pharmacopoeia Commission (IPC) Ghaziabad was used for data collection keeping all the norms of confidentiality.

Treatment was initiated as per national guideline in India, according to which fixed dose combination of two NRTIs (zidovudine/tenofovir + lamivudine) and one NNRTI (nevirapine/efavirenz) is recommended.[4] Each reported case of dermatological ADR was assessed for its causality by using Naranjo's probability scale.[5] Preventability was assessed using Schumock and Thornton preventability criteria.[6] and severity was assessed using the modified Hartwig and Siegel scale.[7] Predictability assessment was done on the basis of modified guidelines developed by the Council for International Organizations of Medical Sciences.[8]

Statistical analysis: For the analysis of data statistically whether the observations are statistically significant or not various statistical parameters like mean, standard deviation were used. For assessing the various risk factors for the development of ADRs mean value of the risk factors were compared between the two groups by using t- test. To see the association between the two variables chi-square test was also used. Calculation of mean and standard deviation was done by using Microsoft excel 2010. For applying t- test and chi-square test we used graph-pad software. In testing the statistical significance between the two means, the level of significance alpha =0.05 was used.

Results

The present study was conducted at Anti-retroviral therapy centre under department of internal medicine, G.S.V.M Medical College, Kanpur in association with department of pharmacology of tertiary care teaching hospitals in Uttar Pradesh, India.

A total no of 250 patients encountered various types of ADRs during the study period. Total number of ADRs recorded was 452. Out of total ADRs (n=452) recorded, 10.8% (n=49) were dermatological ADRs. (Figure-1).

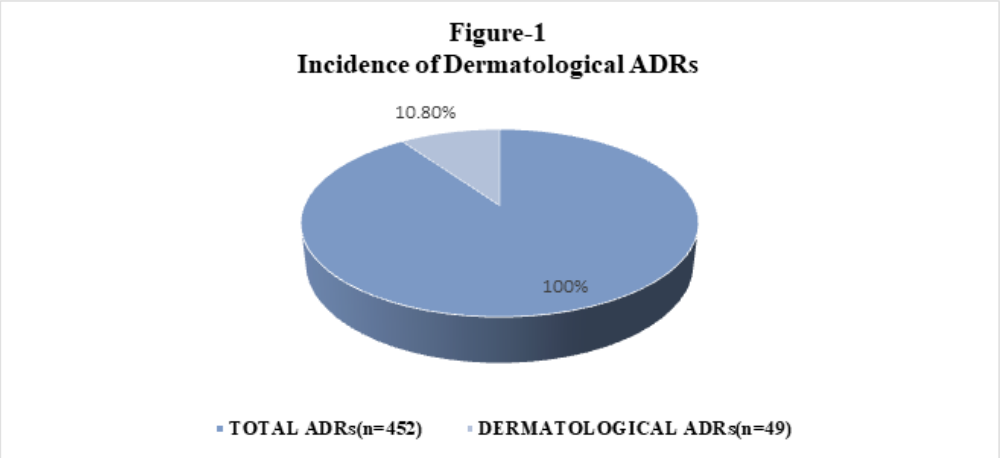

Figure 1: Incidence of dermatological ADRs

Distribution of dermatological ADRs: In our study, among the various dermatological ADRs due to anti-retroviral therapy, most common ADR encountered was Skin rash followed by generalized pruritus, stevens Johnson syndrome & alopecia. (Table-1, Figure-2)

Table 1: Distribution of dermatological ADRs

S. No.	Dermatological ADRs	No.	% of ADRs
1	Rash	43	88%
2	Generalized Pruritus	4	8%
3	SJS	1	2%
4	Alopecia	1	2%
	TOTAL	**49**	**100%**

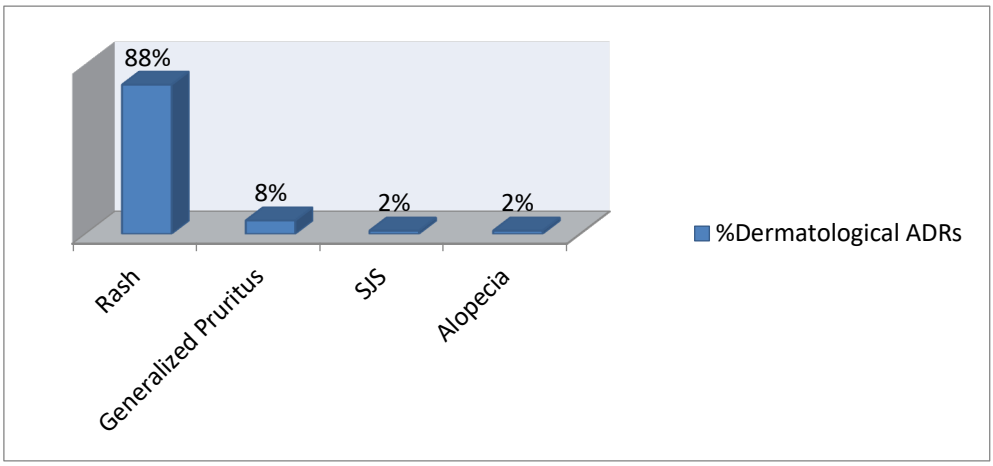

Figure 2: Distribution of dermatological ADRs

Frequency of Dermatological ADRs due to various anti-retroviral drug regimens: In our study maximum burden of dermatological ADRs was found due to regimen ZLN followed by TLE, TLN, and ZLE. (Table-2, Figure-3). In our study no dermatological ADR was encountered due to regimen ZLAT/r.

Table 2:Dermatological ADRs due to different Anti-retroviral Regimens

S. No.	Regimen	Dermatological ADRs No.	% of ADRs
1	ZLN	34	69.38%
2	TLE	10	20.4%
3	TLN	3	6.1%
4	ZLE	2	4%
5	ZLAT/r	0	0%
	Total	**49**	**100%**

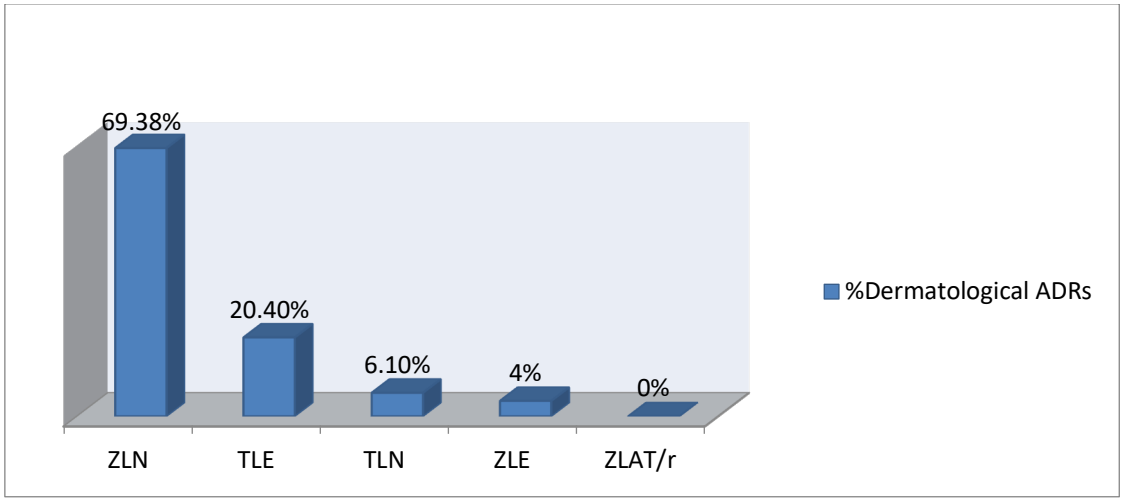

Figure 3: Dermatological ADRs due to different Anti-retroviral Regimens

Analysis of various risk factors for development of Dermatological ADRs due to Anti-retroviral therapy: The details of analysis are shown in the following **table-3.**

Table 3:

S. No.	Characteristics	Dermatological ADRs					
		YES (n=46)		NO (n=204)		Test Result	P value
		MEAN	SD	MEAN	SD		
1	**Gender**						
	Male	14		93		$\chi 2=3.52$	0.06
	Female	32		111			
2	**Age(yr.)**	36.93	10.91	35.46	9.07	t=0.85	0.34
	<20	17.5 (n=2)	0.70	14 (n=6)	4.09	t=0.34	0.29
	21-40	31.75 (n=28)	5.85	31.91 (n=143)	4.92	t=0.03	0.87
	41-60	46.28 (n=14)	4.68	46.77 (n=54)	4.47	t=0.080	0.71
	>60	63.5 (n=2)	2.12	n =1			
3	**weight (k.g.)**	49.73	8.58	49.50	8.73	t=0.16	0.87
	<35	33 (n=3)	2.64	31.6 (n=10)	3.83	t=0.16	0.57
	36-55	47.71 (n=32)	5.41	47.02 (n=149)	4.84	t=0.66	0.47
	56-75	60.18 (n=11)	4.68	61.38 (n=44)	4.43	t=0.17	0.43
	>75	n =0		n=1			
4	**CD4 Count (cells/mm3)**	286.58	85.44	256.18	70.74	t=2.24	0.02
	<250	216.39 (n=23)	22.54	218.21 (n=119)	16.70	t=0.025	0.65
	>250	356.78 (n=23)	64.20	313.34 (n=85)	52.26	t=3.36	0.001**
5	**Regimen**	No. of	patients	No. of	patients		
	Nevirapine based	37		124		□2=6.60	0.03*
	Efavirenz based	9		76			
	ZLAT/r	0		4			

Age-$\chi 2=5.57$, $p>0.05$ Weight- $\chi 2=0.57$, $p<0.05$*

From the above table it can be concluded that there was no significant difference observed in gender, age and weight between two groups. However statistically significant difference in between two groups was observed in CD4 count and regimen. Mean CD4 count (286.58 cells /mm3) in the group developing dermatological ADRs was significantly higher than the mean CD4 count (256.18 cells/mm3) in the group who did not encounter dermatological ADRs. CD4 count >250 was observed as a risk factor for developing dermatological ADRs and it was statistically very significant (p<<<0.05, 95% CI) Maximum burden of dermatological ADRs was found in patients who were on nevirapine based regimen and it was found statistically significant (p<0.05, 95% CI).

So; it was observed that CD4 count >250 and nevirapine based regimen were risk factors in our study for developing dermatological ADRs.

Distribution of ADRs according to ADR types:

All reported ADRs were categorized into six types according to expanded Rawlins & Thompson classification. Majority of dermatological ADRs were of type-B in our study.

Causality assessment of ADRs:

All ADRs were analysed for the causality according to Naranjo probability scale. Out of total 49 dermatological ADRs majority were in probable category followed by possible category. There was no ADR which was classified as doubtful or definite category. (Table-4, Figure-4).

Table 4: Causality of ADRs (Naranjo Probability Scale)

Probability Category	No. of Dermatological ADRs	% of ADRs
Definite	0	0%
Probable	43	87.75%
Possible	6	12.25%
Doubtful	0	0%
TOTAL	49	100

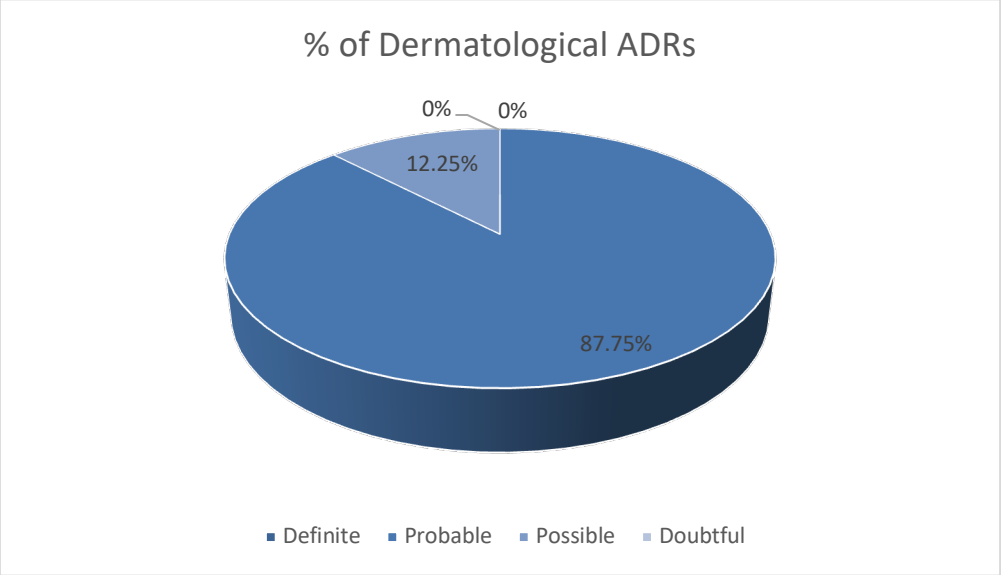

Figure 4: Causality of ADRs (Naranjo Probability Scale)

Severity Assessment of ADRs: All reported ADRs were analysed for severity according to modified Hartwig severity scale. Out of total reported dermatological ADRs majority were of mild type followed by moderate and severe. (Table-5. Figure-5)

Table 5: Severity of ADRs (Modified Hartwig severity scale)

Severity Level	No. of Dermatological ADRs	% of ADRs
Mild	42	85.71%
Moderate	6	12.24%
Severe	1	2.04%
TOTAL	**49**	**100%**

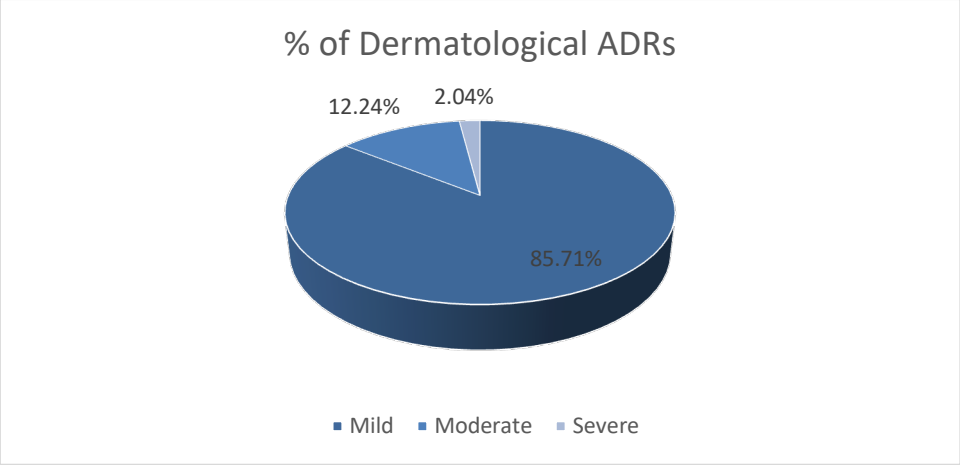

Figure 5: Severity of ADRs (Modified Hartwig severity scale)

Seriousness Assessment of ADRs: All reported dermatological ADRs were assessed for seriousness as per criteria given by W.H.O. Majority of dermatological ADRs were found non-serious in our study. Only single case of stevens johnson syndrome was serious type in our study. Figure-6

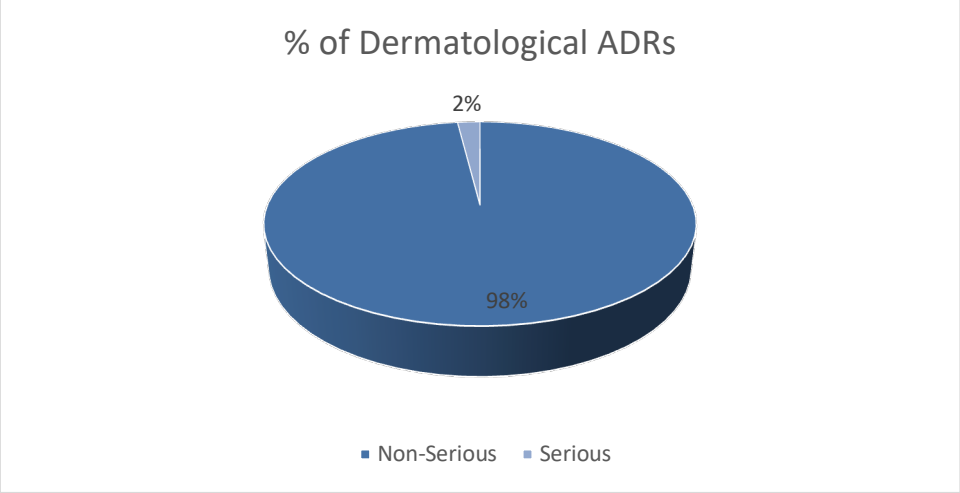

Figure 6: Seriousness of ADRs (W.H.O. Criteria)

Assessment of Predictability of ADRs: All ADRs were analysed for predictability according to modified guidelines given by the Council for International Organizations of Medical Sciences (CIOMS). Out of total 49 dermatological ADRs majority were predictable. Only single case of ANOSMIA in patient on TLE regimen was unpredictable. Figure-7

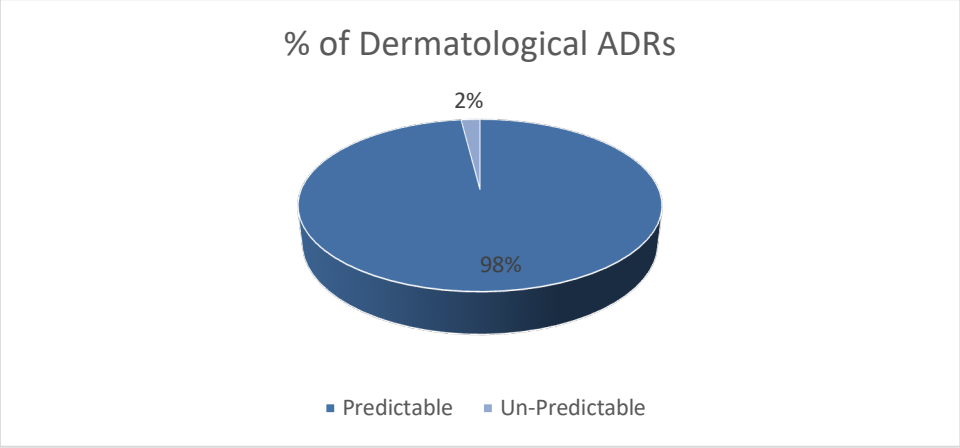

Figure 7: Predictability of ADRs (CIOMS Guidelines)

Assessment of outcome of ADRs: All ADRs were analysed for outcome using WHO criteria. Out of 49 dermatological ADRs majority of cases has been recovered. Only two cases of severe skin rashes were in recovering phase and single case of alopecia was in continuing phase in our study. Figure-8

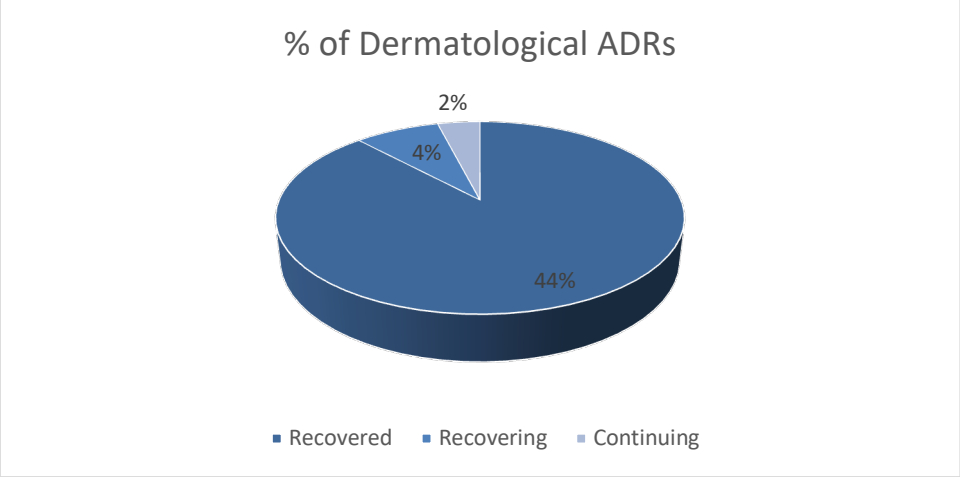

Figure 8: Outcome of ADRs (W.H.O. Criteria)

Assessment of Preventability of ADRs: All ADRs were analysed whether they are preventable or not. Modified Schumock Thornton Preventability Criteria was used for preventability assessment. All dermatological ADRs were Non preventable type in our study.

Discussion

Occurrence of 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. In our study frequency of dermatological ADRs was more among females than males which was found statistically significant. This finding is in line with study done by Zahoor A. Rather et al[9] and Emmanuel et al[10] but not with a study done by Anshu Kumar Jha[11] Most plausible reason for this finding may be due to that clearance of nevirapine is about 25% lower and Cmax is about 44% higher in females than males and other gender related differences in pharmacokinetic, immunological and hormonal factors[12]. Majority of patients were middle aged (21 to 40 years). This finding is in accordance with the study done by Padukadan et al[13] and Emmanuel et al[10] where in the mean age group was 41+/- 11.36 years.8 This could be because HIV is more prevalent in the adult population.

The most common dermatological ADR was rash followed by generalized pruritus. This is in concordance with studies done by SA Coopman et al[14], Gail Todd et al [15], Thakkar et al[16] and Modi et al[17] where in the most common presentation was maculopapular rash followed urticaria in HIV patients but not with study done by Akpinar et al[18] where angioedema and urticaria followed by maculopapular rash was most common ADRs. In our study maximum burden of dermatological ADRs was seen due to nevirapine containing regimens than the efavirenz containing and second line regimens. This finding is in concordance with a meta-analysis by Schubber et al[19] shown that patients using NVP are more likely to experience drug hypersensitivity and severe hypersensitivity reactions compared to patients using EFV. Study conducted by Vitezica ZG et al[20] suggest that HLA-DRB1*01 allele plays an important role in susceptibility to NVP and EFV cutaneous reactions. This theory might be the cause of difference in incidence rate of NNRTI-related rash among. Another plausible reason behind this may be that nevirapine is a lipid soluble drug and concentrates more in skin in the form of sulphate metabolite. So causes more dermatological toxicity.

In our study frequency of dermatological ADRs was significantly greater in the patients with CD4 count >250 than the patients who had CD4 count <250. Studies conducted by Knobel H etal, Kiertiburanakul S.et al, AnanworanichJ etal, Manosuthi W et al [21-24] have reported the increasing tendency for NVP hypersensitivity reaction along with the increase of CD4 lymphocyte counts. The underlying theory of this phenomenon is unclear but probably involves cytokine of Th1 and Th2, when the balance of these two was disrupted causing abundant amount of Th2 and therefore enables hypersensitivity reaction to take place. Manosuthi et al [24] showed that every increment of 50 cells/mL of baseline CD4 lymphocyte counts was associated with 1.2 fold likelihood of developing NVP-associated rash. Another potential explanation behind this finding is that NNRTI induced skin rash has cell mediated

immune mechanism. Rapid reversal of immune dysfunction can cause an immune response towards NNRTI antigen and manifest itself in skin rash. This is just like immune reconstitution syndrome as seen in HIV/AIDS patients due to recovery of immune function. In our study majority had a probable (87.75%) causality followed by possible (12.25%) causality according to Naranjo scoring system which is in concordance with a study done by Anshu Kumar Jha et al [11] in which they had a probable causality of 66.04% and a possible causality of 33.96%.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 (85.71%) followed by moderate (12.24%) and severe (2.04%) drug reaction. It is in accordance with study done by Mukherjee et al.[25] and Shah NS et al.[26]

Conclusion

Although the mortality from HIV has significantly decreased due to availability of highly active antiretroviral therapy, there has been a concurrent increase in the incidence of dermatological drug reactions. Female gender, baseline CD4 absolute count above 250 cells/mm3, were predictors for nevirapine-associated rash in HIV patients. We suggest that more stringent evaluation and monitoring should be carefully done in all HIV/AIDS patients who will receive and on NVP therapy, especially if they have the above predictors.

Timely identification of these ADRs, stopping of the offending drug and prompt treatment at the earliest is advised as these severe dermatological ADRs are associated with internal organ damage. This study had several limitations. First, we did not assess the use of concomitant therapy beside ART, which may had cause hypersensitivity reaction in patients. Second, some possible risk factors such as previous history of drug allergy and baseline viral load number were not included in the present study. Last elucidation of underlying cellular and molecular mechanisms of dermatological ADRs due to anti-retroviral therapy is the need of future research.

References

1. AtuahKN, Hughes D, Pirmohamed M. Clinical pharmacology: special safety considerations in drug development and pharmacovigilance. Drug Saf. 2004; 27: 535-5.
2. Wu TY, Jen MH, Bottle A, Molokhia M, Aylin P, Bell D, et al. Ten-year trends in hospital admissions for adverse drug reactions in England 1999–2009. JR Soc Med. 2010; 103:239–50.
3. Holly A., Ward, Glenn G., Rasso, Joseph Shrum. Cutaneous manifestations of antiretroviral therapy J Am Acad Dermatol 2002; 46 :284-93.
4. National AIDS Control Organization. Antiretroviral Therapy Guidelines for HIV-infected Adults and Adolescents. New Delhi: Ministry of Health and Family Welfare, Government of India; May2013. Available from:http://naco.gov.in/sites/default/files/Antiretroviral%20Therapy%20Guidelines%20for%20HIV-Infected%20Adults% 20and% 20Adolescents. pdf.
5. Naranjo CA et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981; 30: 239-45.
6. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm. 1992; 27: 538.
7. Hartwig SC, Siegel J et al. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992; 49: 2229-32.
8. Council for international organization for medical science (1994) WGI. Guidelines for preparing core clinical safety information on drugs. Council for international organization for medical sciences, Geneva.
9. Rather, et al.: Gender differences in the toxicity profile of antiretroviral drugs Indian Journal of Pharmacology | April 2013 | Vol 45 | Issue 2
10. Kouotou EA, Nansseu JR, Ngono VN, Tatah SA, Bissek ACZK, Ndam ECN, et al. Prevalence and Clinical Profile of Drug Eruptions among Antiretroviral Therapy-Exposed HIV Infected People in Yaoundé, Cameroon. Dermatol Res Pract. 2017; 2017:1–6.
11. Shenoy AK, Chowta MN, Gadgade A, Jha AK, Ramapuram JT. Evaluation of adverse drug reactions in HIV positive patients in a tertiary care hospital. Perspect Clin Res. 2015;6(1):34–8.
12. Rademaker M. Do Women Have More Adverse Drug Reactions? Am J Clin Dermatol. 2001; 2(6):349–51.
13. Padukadan D, Thappa DM. Adverse cutaneous drug reactions: Clinical pattern and causative agents in a tertiary care centre in South India. Indian J Dermatol Venerol Leprol. 2004; 70:20–4.
14. Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous Disease and Drug Reactions in HIV Infection. N Engl J Med. 1993; 328(23):1670–4.
15. Todd G. Adverse Cutaneous Drug Eruptions and HIV: a Clinician's Global Perspective. Dermatol Clin. 2006; 24(4):459–72.

16. Thakkar S, Patel T.K, Vahora R. Cutaneous adverse drug reactions in a tertiary care teaching hospital in India: An intensive monitoring study. Indian J Dermatol. 2017; 62(6):618–25.
17. Modi A, Desai M, Shah S, Shah B. Analysis of cutaneous adverse drug reactions reported at the regional ADR monitoring center. Indian J Dermatol. 2019; 64(3):250.
18. Akpinar F, Dervis E. Drug eruptions: An 8-year study including 106 inpatients at a dermatology clinic in Turkey. Indian J Dermatol. 2012; 57(3):194–8.
19. Shubber Z, Calmy A, Andrieux-Meyer I, Vitoria M, Renaud-Théry F, Shaffer N, et al. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy. AIDS. 2013; 27(9): 1403–12.
20. Vitezica ZG, Milpied B, Lonjou C, Borot N, Ledger TN, Lefebvre A, et al. HLA-DRB1*01 associated with cutaneous hypersensitivity induced by nevirapine and efavirenz. AIDS. 2008; 22:539–44.
21. Knobel H, Guelar A, Montero M, Carmona A, Luque S, Berenguer N, et al. Risk of side effects associated with the use of nevirapine in treatment-naive patients, with respect to gender and CD4 cell count. HIV Med. 2008; 9:14–8.
22. Kiertiburanakul S, Sungkanuparph S, Charoenyingwattana A, Mahasirimongkol S, Sura T, Chantratita W. Risk factors for nevirapine-associated Rash Among HIV-infected patients with low CD4 cell counts in resource-limited settings. Curr HIV Res. 2008; 6:65–9.
23. Ananworanich J, Moor Z, Siangphoe U, Chan J, Cardiello P, Duncombe C, et al. Incidence and risk factors for rash in Thai patients randomized to regimens with nevirapine, efavirenz or both drugs. AIDS. 2005; 19: 185–92.
24. Manosuthi W, Sungkanuparph S, Tansuphaswadikul S, Inthong Y, Prasithsirikul W, Chottanapund S, et al. Incidence and risk factors of nevirapine-associated skin rashes among HIV-infected patients with CD4 cell counts <250 cells/μL. Int J STD AIDS. 2007; 18:782–6.
25. Mukherjee S, Era N, Saha B, Tripathi SK. Adverse drug reaction monitoring in patients on antiretroviral therapy in a tertiary care hospital in Eastern India. Indian J Pharmacol. 2017; 49(3):223–8
26. Shah NS, Chauhan SP, Desai MK, Shah A. A safety analysis of different drug regimens used in human immunodeficiency virus- positive patients. Indian J Sex Transm Dis AIDS. 2018; 39(2):84–90.