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Dermatology Section

Clinical Profile of Cutaneous Adverse Drug Reactions in HIV Patients: A Cross-sectional Study

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ABSTRACT

Introduction: Cutaneous Adverse Drug Reactions (cADRs) are one of the most common clinical presentations in patients with Acquired Immunodeficiency Syndrome (AIDS). These patients are more prone to developing cADRs due to various factors such as altered drug metabolism, immune dysregulation, genetic predisposition, polypharmacy, and oxidative stress. Therefore, a methodical study of cADRs, including risk factors, patterns of drug eruption, and prognostic factors, is of crucial clinical significance.

Aim: To determine the prevalence of cutaneous drug reactions in Human Immunodeficiency Virus (HIV) patients and also study the various patterns of cADRs.

Materials and Methods: This cross-sectional study was conducted at the outpatient department of Infectious Diseases and Medical Centre, Voluntary Health Services, Chennai, Tamil Nadu, India, from April 2020 to December 2020. A total of 150 HIV patients above 18 years who were taking Anti Retroviral Therapy (ART) were included in this study. After screening for cADRs, it was classified as Morbilliform Eruption, Erythema Multiforme, Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Fixed Drug Eruption (FDE), etc. The severity of the reaction was graded based on the Modified Hartwig and Siegel severity assessment scale. Pearson Chi-square test and Bivariate Pearson Correlation were performed to statistically analyse the data.

Results: Among the total of 150 HIV patients (87 males and 63 females), the mean age of the study population was 41.07 years. There was a male predominance with a male-to-female ratio of 1.3:1. About 44% (n=6) of the study population had opportunistic infections. The prevalence of drug eruptions in this study was found to be 6% (n=9). Out of which, 55.6% (n=5) of the population had a morbilliform eruption, and 22.7% had urticarial (n=2) and pruritus (n=2), respectively. About 56% (n=5) of the drug reactions were caused by the Tenofovir/Lamivudine/Efavirenz regimen, and the remaining 44% (n=4) of the drug eruptions were caused by the Abacavir/Lamivudine/Dolutegravir regimen.

Conclusion: The prevalence of drug eruptions in this study was 6%, and the majority of the population had a morbilliform eruption.

Keywords: Human immunodeficiency virus, Immune response, Oxidative stress, Skin reaction

INTRODUCTION

In 1987, Zidovudine (AZT), the first antiretroviral drug, was made available to AIDS patients [1]. Since 2004, a stable and effective combination therapy, Highly Active Antiretroviral Therapy (HAART), has been available free of cost in India [1]. With the increasing application of HAART throughout the world, the quality of such patients' lives has improved, their survival time has been prolonged, and the lives of numerous AIDS patients have been saved [1]. However, HAART regimens cannot purge the HIV-1 virus in patients and completely cure AIDS, and side-effects occur with clinical therapies, which in turn may lead to the patient's termination of treatment and, sometimes, even death [1]. Although HAART reduces the occurrence of mucocutaneous disorders in HIV-1-infected patients [2,3], the treatment regimen itself may be the cause of a common side-effect, drug eruption [4].

Due to the immunosuppression experienced by AIDS patients, they are exposed to a variety of opportunistic infections and tumors, which makes them more susceptible to several types of antibiotics, antifungal drugs, antivirals, and even antitumor drugs, thereby increasing the chances of drug eruption [5,6]. Cutaneous Adverse Drug Reactions (cADRs) are one of the most common clinical presentations in patients with HIV/AIDS. They are more prone to experiencing cADRs due to various factors such as altered drug metabolism, immune dysregulation, genetic predisposition, polypharmacy, and oxidative stress [5].

These drug eruptions may reduce a patient's quality of life and adversely affect treatment adherence, finally leading to treatment failure. However, the risk factors of cADRs in AIDS patients are not well understood. Therefore, a systematic study of cADRs, including predisposing factors, patterns of drug eruption, and drug eruption-related factors influencing prognosis, is of crucial clinical significance. Studies in the literature regarding cADRs with the newer ART regimens are lacking. This study aims to shed light on cADRs associated with newer ART regimens. With this aim, the present study was conducted to determine the prevalence of cutaneous drug reactions in HIV patients and to study the various patterns of drug reactions.

MATERIALS AND METHODS

This cross-sectional study was conducted in the outpatient department of Infectious Diseases and Medical Centre, Voluntary Health Services, Chennai, Tamil Nadu, India, from April 2020 to December 2020. The study commenced after obtaining approval from the Institutional Ethical Committee (VMKVMC&H/IEC/19/08).

Inclusion criteria: All consecutive HIV patients aged above 18 years, who started on ART during the study period, were included.

Exclusion criteria: Patients who were not willing to participate in the study and refused to provide consent were excluded.

Procedure

Total of 150 HIV patients were included sufficing the inclusion and exclusion criteria. After obtaining informed consent from all participants, baseline information regarding demographic features (age, sex), duration of illness and symptoms, previous history of any drug eruption, drugs taken and complications any were recorded

in a pre-tested structured proforma. Previous history of cutaneous reactions was confirmed by medical records. The most recent CD4+counts of each patient were recorded from the patient's medical records.

Each patient was then subjected to a complete dermatological examination including skin, hair, nail and mucosa in adequate day light. The diagnosis of the pattern of drug eruption was made based on clinical features. After screening for cADRs, it was classified under any of the following categories for the purpose of analysis: 1) Morbilliform eruption; 2) Erythema multiforme; 3) SJS; 4) TEN; 5) FDE; 6) Urticaria; 7) Pruritus; 8) Vasculitis; 9) Erythroderma; 10) Photodermatoses; 11) Diffuse cutaneous pigmentation; and 12) Drug hypersensitivity syndrome.

The severity of the reaction was graded based on Modified Hartwig and Siegel severity assessment scale [7]. The modified Hartwig and Siegel scale grades the severity of drug eruption into mild, moderate or severe with various levels depending upon the factors like requirement for change in therapy, duration of stay in hospital, and the disability produced by such drug eruption. As per the scale, the level of severity of cADRs was classified as levels 1-7:

- Levels 1 and 2 indicate mild,
- Levels 3, 4a, and b moderate,
- Levels 5, 6, and 7 severe grade [7]. The association between the prevalence of eruption and effects of gender, education, occupation and history of allergy was investigated. The findings were recorded in a proforma for analysis and interpretation of data.

STATISTICAL ANALYSIS

Data was entered using International Business Management (IBM) Statistical Package for Social Sciences (SPSS) version 23.0. Pearson chi-square test was used to find an association between the prevalence of eruption in HIV positive patients and ART regimens. Their association significance was determined at $p<0.05$. The analytical relation was established between CD4 count and prevalence of eruption.

RESULTS

In this study, out of total 150 HIV patients, 87 (58%) patients were males and 63 (42%) were females and there was a male preponderance and the male to female ratio is 1.3:1. Majority of the study subjects were in the age group of 40-60 years, with a mean age of 41.07±5 years. Most of them have completed high school, majority were unemployed and resided in urban area. In this study, majority of the patients 129 (86%) acquired the infection through sexual mode followed by 14 (9.3%) patients who acquired the infection through needles and 7 (4.7%) of patients through blood transfusion. Out of the 150 patients, 6 (4%) had past history of allergy to drugs. The World Health Organisation (WHO) clinical staging of the study population showed that majority of them were in Stage-1, followed by Stage-3, Stage-2 and Stage-4. Most of the patients 78 (52%) had CD4 count between 200-500 and 26 (17%) had count below 200. Among the study population, 66 (44%) had a past history of opportunistic infections which included Pulmonary Tuberculosis (TB) in 16 (23.9%) and oral candidiasis in 16 (23.9%) followed by a combination of Pulmonary TB and Oral Candidiasis in 3 (4.5%), Herpes simplex infection in 10 (15%), Herpes zoster in 7 (11%), pneumocystis pneumonia in 5 (7.6%), cryptococcal meningitis in 4 (6%) patients, Extrapulmonary TB in 3 (4.5%) and cerebral toxoplasmosis in 2 (3%) patients [Table/Fig-1].

All the study subjects were on ART. Most of the patients 66 (44%) were on TDF (Tenofovir)+3TC (Lamivudine)+DTG (Dolutegravir) regimen followed by 59 (39.3%) patients who were on TDF+3TC+EFV (Efavirenz) regimen. There were 14 types of ART regimens in this study. Statistical analysis depicted that there was no association between ART regimens and prevalence of eruption [Table/Fig-2].

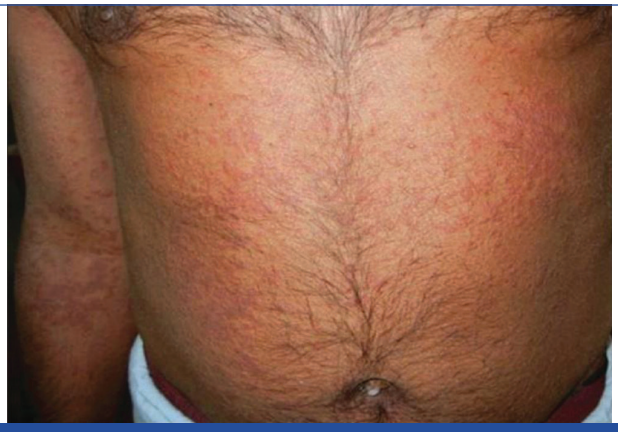
S. No.	Parameter	Variables	N=150
1	**Age (years)**	18-39	68 (45.3)
		40-59	78 (52)
		>60	4 (2.7)
2	**Sex**	Male	87 (58)
		Female	63 (42)
3	**Education**	Completed high school	82 (54.6)
		Middle school	5 (3.3)
		Primary school	48 (32)
		Illiterate	15 (10)
4	**Occupation**	Semi-skilled worker	7 (4.7)
		Skilled worker	45 (30)
		Unemployed	57 (38)
		Unskilled worker	41 (27.3)
5	**Residence**	Rural	67 (44.7)
		Urban	83 (55.3)
6	**Marital status**	Married	102 (68)
		Separated	10 (6.7)
		Unmarried	25 (16.7)
		Widow	13 (8.7)
7	**Mode of transmission**	Blood transfusion	7 (4.7)
		Sexual mode	129 (86)
		Through needles	14 (9.3)
8	**History of drug allergy**	Yes	6 (4)
		No	144 (96)
9	**WHO staging**	Stage-I	60 (40)
		Stage-II	29 (19.3)
		Stage-III	38 (25.3)
		Stage-IV	23 (15.3)
10	**CD4 count**	0-200	26 (17.3)
		200-500	78 (52)
		>500	46 (30.7)
11	**Opportunistic infection**	Yes	66 (44)
		No	84 (56)

[Table/Fig-1]: Demographic profile of the study population.
WHO: World health organisation

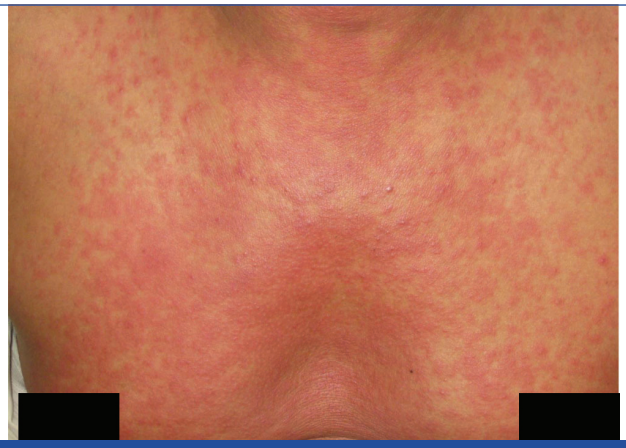
ART regimen	Frequency	Percentage	Prevalence of drug eruption n (%)	p-value
3TC+TDF+EFV	59	39.3	5 (56%) (Morbilliform eruption)	0.998
ABC+3TC+DTG	2	1.3	4 (44%) (pruritus and urticaria)	0.232
ABC+3TC+EFV	2	1.3	0	-
ATZ+3TC+EFV	1	0.7	0	-
TDF+3TC+DRV/r+DTG	1	0.7	0	-
ABC+3TC+RAL	1	0.7	0	-
TAF+FTC+DTG	2	1.3	0	-
ATV/r+DTG	1	0.7	0	-
TDF+3TC+ATZ/r	1	0.7	0	-
TDF+3TC+DTG	66	44.0	0	-
TDF+3TC+RPV	4	2.7	0	-
TDF+FTC+DTG	5	3.3	0	-
TDF+FTC+EFV	3	2.0	0	-
TDF+FTC+RTV+DRV	1	0.7	0	-
TDF+3TC+LPV+RTV	1	0.7	0	-
Total	150	100.0	9 (100%)	-

[Table/Fig-2]: Various Anti-retroviral Therapy (ART) regimens among the study population and the prevalence of drug eruption.
Chi-square test
TDF: Tenofovir disoproxol fumarate; 3TC-Lamivudine; EFV: Efavirenz; ABC: Abacavir; DTG: Dolutegravir; DRV/r: Darunavir/ritonavir; RAL: Raltegravir; TAF: Tenofovir alafenamide; ATV/r: Atazanavir/Ritonavir; RPV: Rilpivirine; FTC: Emtricitabine; RTV: Ritonavir; LPV: Lopinavir

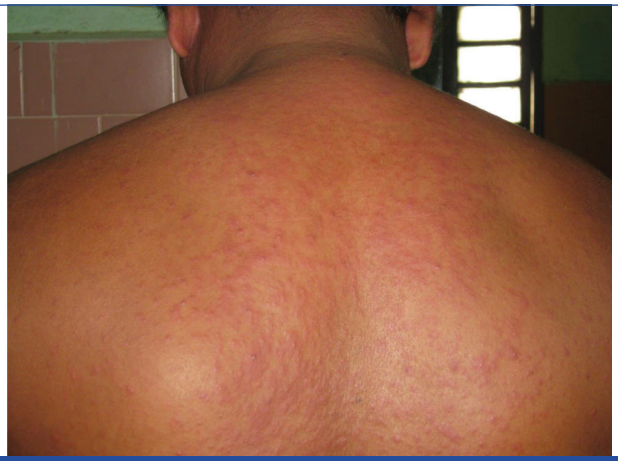
Only 2 (1.3%) patients presented with nail abnormality and both had koilonychia. About 12 (8%) of the patients had systemic involvement out of which six (50%) patients experienced giddiness, three (25%) had fever, two (16%) had hepatitis and only one (8%) of patients had nausea/vomiting. The prevalence of drug eruption in this study was 6%. A total of nine patients had drug eruption out of which, five (55.6%) patients had morbilliform eruption [Table/Fig-3-5], two (22.7%) had urticaria [Table/Fig-6,7] and two (22.7%) had intractable pruritus.



[Table/Fig-3]: Morbilliform eruption on abdomen and forearms of a male patient.



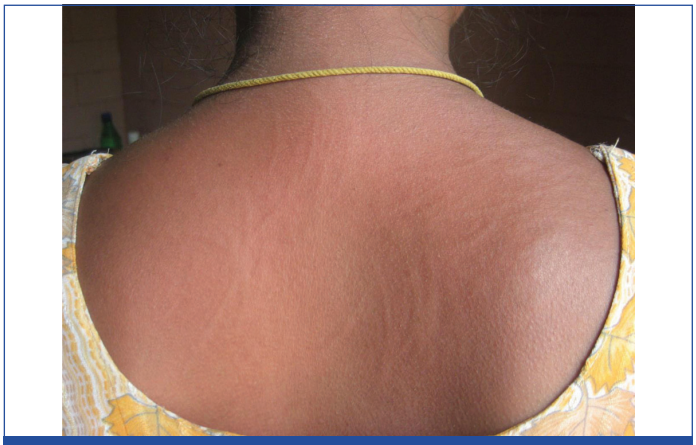
[Table/Fig-4]: Morbilliform eruption on neck and chest region of female patient.



[Table/Fig-5]: Morbilliform eruption on back region of male patient.

Out of the nine patients who had drug eruption, five (55.6%) patients were on TDF+3TC+EFV regimen and four (44.4%) patients were on ABC+3TC+DTG. All the five patients who were on TDF+3TC+EFV regimen had morbilliform eruption. Urticaria and pruritus developed on patients who were on ABC+3TC+DTG regimen.

In present study, there was a significant association between prevalence of eruption and gender as well as past history of allergy [Table/Fig-8]. However, the association between prevalence of eruption and age, education, occupation, marital status, residence, mode of transmission, opportunistic infections as well as WHO staging were not significant (p>0.05).



[Table/Fig-6]: Urticaria on back region of female patient.

[Table/Fig-7]: Urticaria on forearm region of female patient.

		Prevalence of eruption		p-value
		Yes (n=9)	No (n=141)	
Sex	Female	8	55	**0.004**
	Male	1	86	
Total		9	141	

[Table/Fig-8]: Association between sex and prevalence of drug eruption.
Chi-square test

All various types of cADRs in this study were seen in patients with CD4 count less than 200 cells [Table/Fig-9]. A bivariate correlation was used to find the relation between CD4 count and prevalence of drug eruption. The result of analysis showed that there was no significant linear relationship between CD4 count and prevalence of eruption [Table/Fig-10].

		Prevalence of eruption		p-value
		Yes	No	
CD4 count	<200	9	17	0.356
	200-500	0	78	
	>500	0	46	
Total		9	141	

[Table/Fig-9]: Association between CD4 count and prevalence of drug eruption.
N=150 patients; Chi-square test was used to calculate the p-value

Parameters		CD4 count
CD4	Pearson Correlation	1
	Sig. (2-tailed)	0.356
Prevalence of eruption	Pearson Correlation	-.076
	Sig. (2-tailed)	0.356

[Table/Fig-10]: Bivariate correlation between CD4 count and cADRs.
Total N=150 patients

DISCUSSION

The HIV infected persons have to take ART lifelong [5]. The use of ART has been associated with short term and long term adverse effects [8] despite their beneficial effects. These toxicities may reduce patient's quality of life and adversely affect treatment adherence [9-11] and consequently may lead to treatment failure [8]. The management of cADRs to ART with suspected drug discontinuation, dose adjustment or switching to the other ART and supportive treatments are frequent methods that increase the tolerability of ART [6].

Continuous intensive monitoring of cADRs in HIV infected patients who are on ART helps in individualising the pattern of cADRs and helps clinicians to select an ART regimen that is not only effective in achieving, maintaining viral suppression, and improving immune function but also safe in overall HIV management. The rapid detection and treatment of cADRs, plus the identification of the causative agents, are essential for preventing a progression of the reaction [12].

In this study, there was a male predominance which was similar to the studies done by Rajesh R et al., Li YY et al., Kumarasamy N et al., Singh H et al., Alexoudi I et al., and Coopman SA et al., [12-17]. In contrast the studies done by Agu KA et al., and Kouotou EA et al., showed a female predominance [11,18]. Regarding the age, most of the study population in this study belonged to 40-59 years which is similar to the study done by Rajesh R et al., [12]. In studies done by Agu KA et al., Li YY et al., Kumarasamy N et al., Kouotou EA et al., the most common age group was 30-44 years [11,13,14,18]. In study done by Singh H et al., the age group was 25-35 years [15].

In this study, females showed a higher prevalence of drug eruption compared to males. This finding is similar to the studies done by Agu KA et al., Singh H et al., Kouotou EA et al., Maharani PN et al., Modayil RR et al., and Mehta U et al., which showed a female predominance [11,15,18-21]; but contrast to the studies done by Rajesh R et al., Li YY et al., and Alexoudi I et al., which showed a male predominance [12,13,16]. The relation between cADRs and sex was assumed to be influenced by several factors such as body fat percentage, hormonal factor, and enzyme activities [22].

Most of the study subjects in this study acquired the infection through sexual mode of transmission (86%), which was similar to the other studies done in South India [14,23]. The prevalence of drug eruption in this study was found to be 6%. This was comparable to a study done by Li YY et al., [13]. The prevalence was lower in studies done by Kouotou EA et al., Salami TA et al., [18,24], and higher in various other previous comparable studies [Table/Fig-11] [11-15,18,19,23,24]. The lesser prevalence of cADRs in the present study, may be due to the usage of Tenofovir based regimen and more recent ART regimens including integrase inhibitors with better tolerability, enhanced virological efficacy and an overall safer profile. The higher prevalence in other studies may be due to the ART regimens, genetic and geographic factors and more sample size.

Researcher	Study population	Year	Sample size	Prevalence
Kouotou EA et al., [18]	Yaounde, Cameroon	2010-2014	6829	0.6%
Salami TA et al., [24]	Nigeria	2001-2005	900	2.8%
Li YY et al., [13]	Yunnan, China	2011-2013	1817	7.4%
Agu KA et al., [11]	Nigeria	2011 (Jan-Dec)	1237	11.4%
Kumarasamy N et al., [14]	South India	1996-2006	3154	15.2%
Kumarasamy N and associates [23]	South India	2000-2003	333	14%
Rajesh R et al., [12]	Manipal, South India	2009-2012	450	16.5%
Singh H et al., [15]	Chattisgarh, India	2006-2008	79	15.8%
Maharani PN et al., [19]	Indonesia	2014-2018	557	16.9%
Present study	Chennai, South India	2020	150	6%

[Table/Fig-11]: Overall prevalence of cutaneous drug eruption in HIV positive patients from previous comparable studies with present study [11-15,18,19,23,24, present study].

The most common pattern of drug eruption was morbilliform eruption in this study followed by urticaria which was similar to other previous studies [Table/Fig-12] [12,16-19]. Among the various individualised drug eruptions, benign forms of eruption were seen in all the patients in this study. These results are close to that from other studies [19,25,26]. Severe forms of eruption were not seen in this study as we didn't use Nevirapine based regimens.

Researcher	Study population	Year	Sample size	Patterns
Present study	Chennai, South India	2019-2020	150	Morbilliform eruption-55.5% Urticaria-22.2% Pruritus-22.2%
Rajesh R et al., [12]	Manipal, South India	2009-2012	450	Morbilliform eruption-5.4%
Coopman SA et al., [17]	Boston, United States	1988-1991	684	Morbilliform eruption-74% Urticaria-17%
Alexoudi I et al., [16]	Athens, Greece	1988-2003	1324	Morbilliform eruption-40% Urticaria-5.6%
Kouotou EA et al., [18]	Yaounde, Cameroon	2010-2014	6829	Morbilliform eruption-36.6% Fixed pigmented erythema-7.3% Acute urticaria-4.9% Erythema multiforme-4.9% TEN-1% DRESS-1%
Maharani PN et al., [19]	Indonesia	2014-2018	557	Morbilliform eruption-85.6% SJS-8.9% Urticaria-4.4% Erythroderma-1.1%

[Table/Fig-12]: Comparison of various patterns of drug eruption with similar studies done elsewhere [12,16-19, present study].
DRESS: Drug reaction with eosinophilia and systemic symptoms

It was difficult to identify a single drug responsible for drug eruptions since the patients were taking multiple drugs. The ART molecules most likely to induce drug eruptions in the present study were Efavirenz and Abacavir. The percentage of drug eruptions due to Efavirenz was 55.5% in this study. It was very different compared to another study [27]. This was explained by the greater number of patients on Efavirenz containing regimen in this study.

In the literature, several authors recommend continuation of treatment in more than 50% of the patients when it is a benign drug eruption [25]. The same regimen was continued in this study due to the mild form of eruption. In all the patients with drug eruption, the lesions resolved without any modification in the drug regimen. In this study, the patients who had past history of drug allergy were more likely to develop drug eruptions. This was similar to a study done by Li YY et al., [13]. So, before treating patients with new medications, the treating physician should enquire about the history of drug allergy and avoid using the medications or structural analogues of those medicines that cause allergy.

Limitation(s)

The limitations of this study include a lesser sample size which consisted only of adults more than 18 years on ART. In addition,

the study was done at a single centre which makes it difficult to generalise the findings to other population.

CONCLUSION(S)

In this study, the prevalence of drug eruption was found to be 6%. A high number of cases were found in males with low CD4 count. The most common pattern of cADRs was morbilliform eruption. The most common drugs implicated in causing this eruption were Efavirenz and Abacavir. ADRs are much more common in HIV patients than in the general population. These toxicities may lead to a reduced quality of life, affect treatment adherence, and ultimately lead to treatment failure. Patient compliance can be improved with proper education and counselling regarding the disease process and inadvertent side-effects due to ART. The constant improvement and introduction of new drugs in clinical practice will still require careful monitoring for skin reactions and elucidation of the various risk factors for drug eruption occurrence in HIV patients.

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