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Impact of antiretroviral therapy on cutaneous adverse drug reactions in adult HIV patients: A study from a tertiary care hospital

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ABSTRACT

Background: Adverse drug reactions (ADRs) significantly impact public healthcare, especially among HIV patients. These reactions, which range from mild pruritus to severe conditions such as Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), affect the quality of life and treatment outcomes. **Aims and Objectives:** The current study was designed to evaluate the various types of cutaneous ADRs (CADRs) in adult HIV patients undergoing antiretroviral therapy (ART). **Materials and Methods:** A retrospective record-based study was conducted at the Department of Dermatology, Venereology, and Leprosy, Government Medical College/Government General Hospital, Suryapet, Telangana, India. Data from November 2017 to October 2020 were analyzed, focusing on patients over 18 years on ART. Relevant demographic and medical data, including blood tests, liver and renal function, and CD4 counts, were collected. **Results:** Out of 3532 patients on ART, 568 (16.08%) developed CADRs. Females represented 54.2% of these cases. The age group most affected was between 29 and 48 years. The most common ART regimen was Tenofovir + Lamivud in + Dolutegravir, followed by zidovudine-based combinations. Nevirapine-based regimens had a higher association with CADRs, particularly severe reactions such as SJS and TEN. **Conclusion:** A significant proportion of HIV patients on ART experience CADRs, with certain drug combinations posing higher risks. This study highlights the need for careful monitoring and selection of ART regimens to minimize the risk of severe CADRs, thereby improving patient outcomes and quality of life in HIV treatment.

Key words: Antiretroviral therapy; Immunocompromised; HIV; Adverse cutaneous drug reactions; Zidovudine; Nevirapine; Highly active antiretroviral therapy

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INTRODUCTION

The global impact of HIV is substantial, with the World Health Organization (WHO) reporting 37.7 million people living with the virus as of 2020, including 1.5 million new cases in that year alone. Notably, 73% of these individuals had initiated antiretroviral therapy (ART).[1] In India, the HIV epidemic touches approximately 2.3 million individuals, representing a significant public health concern.[1]

Highly active ART (HAART), which consists of a combination of three or more antiretroviral drugs, plays a crucial role in managing HIV. The multi-drug regimen of HAART is specifically designed to inhibit viral replication and prevents the development of resistance by targeting the virus through different mechanisms.[2-5]

However, the use of ART is not without challenges, particularly concerning adverse drug reactions (ADRs).

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Defined by WHO as any noxious and unintended response to a drug occurring at normal dosages,[6] ADRs significantly affect patient well-being and adherence to treatment. While the incidence of ADRs in children is around 1.5%, it jumps to 20–30% in adults. Notably, HIV-infected individuals are at an increased risk of developing ADRs, regardless of age. The spectrum of ADRs in the context of ART is wide, ranging from mild symptoms like maculopapular rash to severe, life-threatening conditions such as toxic epidermal necrolysis (TEN).[7-10]

Aims and objectives

The primary aim of this study is to comprehensively assess the various types of cutaneous ADRs (CADRs) occurring in HIV-infected adult patients who are receiving ART. This includes identifying the prevalence and patterns of CADRs, understanding their severity, and examining their correlation with different ART regimens. By focusing on an adult population (age 18 and above), the study seeks to provide insights into the dermatological challenges faced by this demographic in the context of long-term ART management. This research aims to inform clinical practices and improve patient care by highlighting the need for vigilant monitoring of CADRs in HIV treatment.

MATERIALS AND METHODS

Study design

This research was structured as a retrospective, record-based study, specifically designed to analyze historical patient data.

Study population

The focus of this study was on adult patients (aged 18 years and above) who tested positive for HIV and was undergoing ART. This demographic was chosen to understand the prevalence and patterns of CADRs in a mature population under ART.

Study setting

The investigation was conducted at the Government General Hospital, which is affiliated with the Government Medical College in Suryapet, Telangana, India. This setting was selected due to its comprehensive collection of patient records and its status as a primary care center for HIV patients in the region.

Sample size

The sample size was initially determined based on the existing literature, which reported a 16.25% prevalence of CADRs among adults on ART.[11] Factoring in an absolute error margin of 5%, the initial calculated sample size was 215. However, to enhance the robustness of the study, the sample was expanded to include 568 patient records.

Study period

Data were collected and analyzed over a 3-month period. However, the records reviewed spanned a 3-year timeframe, from November 2017 to October 2020, providing a longitudinal perspective on the prevalence and types of CADRs.

Inclusion criteria

Adult patients

Individuals over the age of 18 years, ensuring the focus remain on the adult population.

HIV positive status

Patients diagnosed with HIV, as the study aims to assess the impact of ART on this specific group.

Undergoing ART

Patients currently receiving ART, to directly correlate the observed CADRs with the therapy.

Exclusion criteria

Minors

Patients below the age of 18 are excluded to focus solely on the adult population's response to ART.

Non-ART medications

Individuals taking medications other than ART for HIV treatment or for other conditions, to isolate the effects of ART on CADRs.

Incomplete medical records

Patients with incomplete medical records, including blood tests, liver and renal function tests, and CD4 counts, as these are essential for evaluating the study's primary variable.

Short-term ART users

Patients have not been on ART for a sufficient period to evaluate the onset of CADRs, if the study design specifies a minimum duration of therapy for inclusion.

Patients with pre-existing severe dermatological conditions

To ensure that observed CADRs are attributed to ART, patients with severe dermatological conditions not related to HIV or ART might be excluded.

Data collection

Comprehensive patient data were gathered from records, which included demographic details, complete blood counts, urine analysis, liver and renal function tests, and CD4 counts recorded before starting ART. These variables were considered essential for understanding the baseline health status of patients and their subsequent reaction to ART.

Data analysis

Data analysis was performed using Microsoft Excel 2010 for general data management and Open Epi Info version 3.30 for statistical analysis. The Chi-square test was employed to assess the significance of categorical variables, particularly in identifying patterns and correlations in CADR occurrences. For continuous variables such as age, mean, and standard deviation were calculated to understand the central tendency and dispersion.

Ethical considerations

This study was conducted in strict adherence to ethical standards. Before commencement, approval was obtained from the Institutional Ethics Committee of the Government Medical College, Suryapet. All patient data were anonymized to maintain confidentiality and protect personal information. Furthermore, the study was designed to ensure that no harm or additional risk was posed to any of the participants. Compliance with ethical guidelines was monitored throughout the study to uphold the integrity and ethical responsibility of the research.

RESULTS

A total of 3532 patients were initiated on ART out of which 16.08% (568 cases) patients developed CADRs.

Out of 568 cases, 54.2% (308) were females and 45.8% (260) were males. About 65.9% (373) of patients were between the age groups of 29 and 48 years, with more of females. The minimum age was 19 years and the maximum age was 71 years. The mean age was 38.97 with a standard deviation of +11.17. Chi-square value is 26.42, at 5° of freedom (DOF), and P<0.05 which was significant (Table 1).

Different types of ART regimens and CADRs are shown in Table 2. Tenofovir+Lamivudin+Dolutegravir was given in 76.8% of the cases (2712), followed by Zidovudine+Lamivudine+Nevirapine (ZLN) in 10.9% of cases (387) and Zidovudine+Lamivudine+Dolutegravir in 4.3% of cases (152).

About 30.98% (176) of nevirapine-based regimens were associated with CADRs. Severe CADRs such as Stevens-Johnson Syndrome (SJS) and TEN were associated more with the nevirapine-based regimen. Among the ZLN regimen, 44.1% (171 out of 387) of cases developed CADRs, 42.5% of cases of the TLE regimen (40/94 cases), and 37.5% (15/40) of cases on the ZLE regimen developed CADRs. Other CADRs associated with different ART regimens are shown in Table 2.

Among 568 CADR cases, the maculopapular rash was seen in 42.8% (243) of cases (Chart 1). Hyperpigmentation of the face and palms was seen in 16.6% (93) cases, oral pigmentation in 11.4% (64) cases, nail pigmentation in 11.4% (64) cases, erythema multiforme in 1.7% (9) cases, SJS in 5.7% (32) of cases (Image 3), SJS/TEN overlap in 1.8% (10) cases, TEN in 1.8% (10) cases, lipodystrophy in 3.9% (22) cases, gynecomastia in 2.6% (14) cases, and lichenoid eruption in 1.3% (7) cases. None of the ART regimes show any significant distribution of CADRs.

Grade I reactions were observed in 48.1% (273) cases, Grade II in 42.8% (243) cases, Grade III reactions in 5.6% (32) cases, and Grade IV reactions in 3.6% (20) cases.

The gap between initiation of therapy and development of CADRs was <1 month in 47.3% (269) cases, between 1 month and 6 months was in 17.1% (97) cases, and more than 6 months in 35.6% (202) cases.

CD4 count was <100 in 9.1% (52) cases, 101–200 in 8.5% (48) cases, 201–300 in 19.7% (112) cases, 301–400 in 27.5% (156) cases, 401–500 in 17.6% (100) cases, and more than 500 in 17.6% (100) cases. Chi-square value was 2.11, at DOF 5, P>0.05, which was not significant. There was no significant difference between the genders with respect to CD4 count (Table 3).

DISCUSSION

The study on CADRs in HIV patients receiving ART offers critical insights into the challenges of managing HIV treatment effectively while minimizing side effects.

Table 1: Age and sex distribution of CADRs

Age in years	Males (%)	Females (%)	Total (%)	P-value
19–28	34 (5.9)	71 (12.5)	105 (18.4)	X^2=26.42, at 5 DOF
29–38	87 (15.4)	112 (19.8)	199 (35.2)	P<0.05
39–48	79 (13.9)	95 (16.8)	174 (30.7)	
49–58	38 (6.7)	17 (2.9)	55 (9.6)	
59–68	13 (2.3)	11 (1.9)	24 (4.2)	
>69	09 (1.6)	2 (0.3)	11 (1.9)	
Total	260 (45.8)	308 (54.2)	568 (100)	

CADRs: Cutaneous adverse drug reactions

Table 2: (a) ART regimens - CADRs

Regimen	No. of cases	M P rash (%)	Skin pig (%)	Oral pig (%)	Nail pig (%)
TLE	94	8.5	6.3	0	3.2
ZLN	387	19.9	5.4	4.8	4.5
TLD	2712	4.7	2.2	1.5	1.2
ZLD	152	7.9	5.9	3.9	4.7
ZLE	40	5.0	2.5	2.5	5.0
TLN	22	13.7	0	0	0
ALD	19	10.5	0	0	0
ALN	3	33.3	0	0	0
TL/ATV/R	17	23.5	0	0	0
ZL/ATV/R	1	0	0	0	0
TL/LPV/R	18	11.1	0	0	0
AL/ATV/R	1	0	0	0	0
LPV/R/DTG	56	7.1	0	0	0
DRV/R/RTLV	10	10.0	0	0	0

Table 2: (b) ART regimens - CADRs (part 2)

Regimen	EMF (%)	SJS (%)	SJS/ TEN (%)	TEN (%)	Lipo Dystrophy (%)	Gynaeco mastia (%)	Lichenoid eruption (%)	Total CADRs (%)
TLE	0	2.1	0	1.1	17.0	4.2	0	42.5
ZLN	1.1	3.1	1.1	1.1	2.0	1.1	1.1	44.1
TLD	0.2	0.5	0.2	0.1	0	0	0.1	10.5
ZLD	0	1.4	0.6	0.6	0	0	0	25.0
ZLE	0	2.5	0	0	15.0	5.0	0	37.5
TLN	0	0	0	0	0	0	0	18.2
ALD	0	0	0	0	0	0	0	10.5
ALN	0	0	0	0	0	0	0	33.3
TL/ATV/R	0	0	0	0	0	0	0	23.5
ZL/ATV/R	0	0	0	0	0	0	0	0
TL/LPV/R	0	0	0	0	0	0	0	11.1
AL/ATV/R	0	0	0	0	0	0	0	0
LPV/R/DTG	0	0	0	0	0	0	0	7.1
DRV/R/RTLV	0	0	0	0	0	0	0	10.0
TOTAL	1.7	5.7	1.8	1.8	3.9	2.6	1.3	100

T: Tenofovir, L: Lamivudine, E: Efavirenz, Z: Zidovudine, N: Nevirapine, D/DTG: Dolutegravir, A: Abacavir, ATV: Atazanavir, R: Ritonavir, LPV: Lopinavir, DRV: Darunavir, RTLV: Raltegravir, SJS: Stevens-johnson syndrome, CADRs: Cutaneous adverse drug reactions, TLD: Tenofovir+Lamivudin+Dolutegravir, ZLD: Zidovudine+Lamivudine+Dolutegravir

Table 3: CD4 count in patients with CADRs

CD4 count	Male	Female	No. of cases (%)	P-value
<100	23	29	52 (9.1)	X^2=2.11, DOF 5, P>0.05
101–200	23	25	48 (8.5)	
201–300	49	63	112 (19.7)	
301–400	77	79	156 (27.5)	
401–500	41	59	100 (17.6)	
>500	47	53	100 (17.6)	
Total	260	308	568 (100)	

CADRs: Cutaneous adverse drug reactions

Despite advancements in ART, CADRs remain a significant concern, impacting patient quality of life and adherence to treatment.

Prevalence of CADRs

The study found CADRs in 16.08% of cases, highlighting their common occurrence in HIV treatment. This prevalence rate aligns with the broader range observed in other studies: 31.57% in Akshaya Srikanth's study,[12] 12.8% in Gupta and Agarwal study,[13] 16.25% in Rukmangathen et al.,'s[11] study, and a high of 44.4% in Ajay Sharma et al.,'s[14] study. The variation in these rates could be attributed to differences in patient populations, the specific ART regimens used, and the duration of the studies.

Gender differences in CADRs

Interestingly, the study observed more CADRs in females (54.2%) than in males (45.8%). This is consistent with existing literature suggesting women are more susceptible to ADRs. This disparity may stem from physiological differences such as variations in body mass, hepatic clearance capacities, and the activity of cytochrome P450 enzymes. These factors influence how drugs are metabolized and eliminated, potentially making women more prone to adverse reactions.[14]

Age and CADRs

The study identified the 29–48 age groups as the most affected, constituting 65.9% of cases. This finding is crucial as it suggests that the working-age population, which is typically more active and has higher responsibilities, is

more susceptible to CADRs. Other studies corroborate this trend, indicating a higher prevalence of CADRs in similar age groups, emphasizing the need for targeted monitoring and management strategies for this demographic.[15]

Drug-specific reactions

A significant finding of the study is the high incidence of CADRs (28.7%) associated with nevirapine-based regimens. Nevirapine, a non-nucleoside reverse transcriptase inhibitor, is known for its effectiveness but also for potential liver toxicity and severe skin reactions such as SJS[16] and TEN.[17]

Types of CADRs observed

The most commonly reported adverse cutaneous drug reactions (ACDR) was maculopapular rash, found in 41.8% of cases. Other notable reactions included hyperpigmentation in various body parts, frequently associated with zidovudine and lamivudine-based combinations. These reactions are not just physically discomforting but can also lead to psychological distress, affecting patients' social interactions, and mental health.[18]

Severe CADRs

Particularly concerning are the severe CADRs such as SJS and TEN, observed in 12.6% of cases on ZLN regimens. These severe reactions are life-threatening and require immediate medical attention. The study's findings on genetic predispositions to these reactions suggest the potential for personalized medicine approaches in HIV treatment.[13]

Lipodystrophy and gynecomastia

The study also sheds light on conditions such as lipodystrophy and gynecomastia, which were observed in 3.9% and 2.6% of cases, respectively. These conditions are particularly concerning as they can lead to long-term physical changes and social stigma, impacting patients' adherence to treatment and overall quality of life.[17]

Timing of CADRs

A critical finding is that nearly half of the CADRs occurred within the 1st month of starting ART, underscoring the need for vigilant monitoring during the initial phase of treatment.[18,19]

CD4 count and CADRs

The study notes a higher occurrence of CADRs in patients with a CD4 count of <500, aligning with the understanding that a lower CD4 count, indicative of a weakened immune system, increases the risk of ADRs.[15]

Overall prevalence of ADRs in HIV patients

The finding that up to 80% of HIV-infected patients might experience ADRs at some point during their treatment highlights the complex interplay of factors such as immune dysregulation, altered drug metabolism, and polypharmacy in HIV treatment.[15]

Limitations of the study

Its retrospective design, which may limit the ability to establish causality between ART regimens and CADRs. The research was conducted in a single tertiary care hospital, potentially limiting the generalizability of the findings to other populations and settings. Additionally, the reliance on medical records for data may introduce bias due to incomplete or inaccurate documentation. Lastly, the study did not account for potential confounding factors such as concurrent medications, comorbid conditions, or individual patient susceptibilities that could influence the development of CADRs.

CONCLUSION

Immune mediated ADRs are 100 times more common in HIV patients. The clinician should have high index of suspicion towards the skin and mucosal lesions in HIV patients who are receiving ART. CD4 cell count, which is a marker of the degree of immunodeficiency, combination of anti-retro viral drugs, and the timing of the initiation of ART are taken into consideration to formulate a rational differential diagnosis. Early diagnosis and treatment of CADRs will prevent further complications such as SJS and TEN and subsequently reduce morbidity and mortality. Patch testing and genetic screening may be useful for diagnosing drug allergies but their implementation will be difficult in resource-poor nations like India.

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