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Highly Active Antiretroviral Therapy Induces Hematological and Dermatological Adverse Drug Reactions in HIV Patients in India

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ABSTRACT

Introduction: In India, HIV patients are at a high risk of developing hematological and dermatological adverse drug reactions (ADRs) leading to financial burden.
Materials and Methods: A prospective observational study was conducted on hematological and dermatological ADRs in a South Indian teaching hospital from October 2011 to October 2012. The definition of ADRs established by the World Health Organization (WHO) was used to assess the causality. Predictability of ADRs was assessed by Micromedex database. Preventability of ADRs was assessed using the Schumock and Thornton criteria. **Results:** A total of 174 HIV patients were enrolled [133 (76.4%) males and 41 (23.6%) females], who reported 99 ADRs to HAART. Of the total ADRs, 70 (70.7%) were reported in males and 29 (29.3%) in females, indicating significantly higher reporting of ADRs in males. 67 of the 99 ADRs were hematological, while the remaining 32 were dermatological. A high number of hematological [40 (59.6%)] and dermatological [15 (46.8%)] ADRs were reported for zidovudine + lamivudine + nevirapine-based HAART regimen. In most of the reported ADRs, the suspected drug was withdrawn. The reported hematological ADRs were as follows: 1) anemia with zidovudine [35 (52.2%)]; 2) pancytopenia with zidovudine [20 (29.9%)]; 3) neutropenia with lamivudine; and 4) leucopenia, bicytopenia, and eosinophilia with zidovudine. Dermatological ADRs were maculopapular rash [7 (21.8%)] with nevirapine-, tenofovir + emtricitabine + efavirenz.
Conclusion: Hematological ADRs was higher than that of dermatological ADRs. Physicians must focus on routine monitoring of all possible risk factors in PLW-HIV for early prevention of hematological and dermatological ADRs to HAART.

INTRODUCTION

Adverse drug reactions (ADRs) to highly active antiretroviral therapy (HAART) is a major health issue worldwide that necessitates prolonged hospitalization (1). People living with human immunodeficiency virus (PLW-HIV) being treated with HAART are at a high risk of developing hematological and dermatological ADRs because of polypharmacy (2). With regard to severity, most ADRs to HAART are mild, some are moderate to severe requiring hospitalization, and

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HAART has substantially increased the quality of life and decreased mortality in PLW-HIV (4), who may present with multiple opportunistic infections (OIs), non-acquired immu-

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nodeficiency syndrome (AIDS)-related malignancies, or comorbid diseases (5). the wide range of polypharmacy prescribed along with HAART for comorbid diseases often leads to ADRs. In fact, ADRs to HAART is the most common reason for discontinuing HAART and intentional non-adherence by the patients themselves (6,7).

HIV infection leads to infectious or noninfectious skin diseases with hematological manifestations accompanied by a decrease in immunity (8). However, in PLW-HIV being treated with HAART, HAART itself causes various hematological and cutaneous dermatological ADRs, which are often not reported or go unnoticed by the treating physician (9). Under-reporting of ADRs to HAART has been cited as a major limitation in recognizing the patterns of ADRs to HAART (10). In India, the National AIDS Control Organization (NACO) provides free HAART for PLW-HIV and related OIs (11). Unfortunately, 85% of Indian PLW-HIV discontinue their treatment with HAART within 8 months because of hematological or dermatological ADRs in addition to social stigma, which leads to non-compliance to HAART (12). Most of the ADRs to HAART can be prevented by educating the patients about HAART-associated adverse effects, which may increase their likelihood to adhere to the HAART regimen in terms of timings. This may help maintain viral suppression and improve the overall immune function in HIV management (13,14). The management of ADRs to HAART should be taken care of by the treating physician during patient follow-ups so as to prevent possible ADRs. The study was aimed to characterize the patterns of hematological and dermatological ADRs to HAART in PLW-HIV with regard to causality outcomes, demographics, predictability, and preventability of the reported ADRs.

MATERIALS AND METHODS

Prospective observational monitoring of hematological and dermatological ADRs to HAART in PLW-HIV was performed at the medicine department of a South Indian teaching hospital from October 2011 to October 2012. The study was approved by the Institutional Ethics Committee (IEC273/2011). PLW-HIV who were admitted to the study hospital were initially routed to the Integrated Counseling and Testing Center as per the NACO guidelines (15) and norms of the National Accreditation Board for Hospitals and Healthcare Providers (16) for pre-test and post-test counseling, mode of transmission, and information on the prevention of HIV/AIDS to promote behavioral change and reduce vulnerability associated with HIV disease. Enrolled HIV-seropositive patients (HIV-SPPs) were intensively monitored by a clinical pharmacist for hematological and dermatological ADRs to HAART during their hospital stay as well as during their follow-ups at the HIV clinic of the study hospital. The study procedure was explained to all enrolled patients, and informed consent was obtained from them before starting the study. Patients with clinically suspected infections were excluded from the study. The ADR definition (17) established by the World Health Organization (WHO) and the Naranjo probability scale (18) were used to assess the causality of reported ADRs to HAART by correlating the time of manifestation of ADRs with that of suspected antiretroviral drug intake. The causality was then reported as definite, probable, or possible as per the Naranjo probability scale. HIV-SPPs being treated with HAART and admitted to the study hospital or being treated in the outpatient department were included. HIV-SPPs who were admitted in the hospital for <24 h as in-patients and those who were on "traditional medicines," such as naturopathy, siddha, ayurveda, unani, and homeopathy, were excluded. Reported ADRs were assessed for predictability based on their incidences reported in the Micromedex database, and ADRs reported ≥1/100 times were considered as "predictable." ADR preventability was assessed using the Schumock and Thornton criteria (19). Outcome of the management of reported ADRs was documented based on symptomatic treatment, seriousness of ADRs, and dechallenge and rechallenge of the suspected antiretroviral medication. The duration to onset of ADRs to HAART was assessed as per WHO recommendations on the pharmacovigilance of antiretroviral medicines (20). Hematological and dermatological ADRs to HAART were reported by a clinical pharmacist to the national pharmacovigilance program.

Demographic data of patients were collected from their case records, treatment charts, and laboratory reports and were analyzed for abnormalities associated with hematological and dermatological ADRs. Other data such as baseline CD4 T-cell counts, employment status, social status, OIs, occurrence of ADRs, HAART regimen implicated for ADRs, concomitant drugs taken by the patient, and duration of HAART were documented using individual case record forms. In addition, the patterns of different hematological and dermatological ADRs to HAART were documented by assessing the causality of reported ADRs.

Statistical analysis: Hematological and dermatological ADRs to HAART were assessed in two groups. All statistical calculations were performed using Statistical Package for Social Sciences (SPSS) version 20. P values < 0.05 were considered as statistically significant.

RESULTS

A total of 174 HIV-SPPs, including 133 (76.4%) males and 41 (23.6%) females, were enrolled in this study. Most of the HIV-SPPs were in the age group of 41–60 years (50%), followed by 21–40 years (46%), and then >60 years (4%). Moreover, most of the enrolled patients did not have alcohol-drinking [97 (55.7%)] and smoking habits [110 (63.2%)]. Further, 110 (63.2%) of the HIV-SPPs were literate and 64 (36.8%) were illiterate, and 130 (74.7%) were employed, whereas 44 (25.3%) were unemployed. The baseline CD4 T-cell count was ≤350 cells/µl in 154 (88.5%) patients, followed by 350–500 cells/µl in 16 (9.2%) patients, and >500 cells/µl in the remaining patients. Demographic characteristics of the patients are shown in Table 1.

Table 1. Demographic characteristic of patients.

Characteristics		Number of patients n = 174 (%)
Gender	Male	133 (76.4)
	Female	41 (23.6)
Age (years)	21–40	80 (46)
	41–60	87 (50)
	>60	7 (4)
Alcoholic status	Social	41 (23.6)
	Never	97 (55.7)
	Habitual	31 (17.8)
	Reformed alcoholic	5 (2.9)
Smoking status	Past smoker	42 (24.1)
	Never	110 (63.2)
	Current smoker	22 (12.7)
Literacy	Literate	110 (63.2)
	Illiterate	64 (36.8)
Employment	Employed	130 (74.7)
	Unemployed	44 (25.3)
Baseline CD4 T-cell count (cells/µl)	≤350	154 (88.5)
	350–500	16 (9.2)
	>500	4 (2.3)

Table 1. Characteristics of reported ADRs

Characteristics		Number of ADRs n = 99 (%)
Gender	Male	70 (70.7)
	Female	29 (29.3)
Age (years)	21–40	43 (43.4)
	41–60	50 (50.5)
	>60	6 (6.1)
Baseline CD4 T-cell count (cells/µl)	≤350	79 (79.8)
	350–500	17 (17.2)
	>500	3 (3.0)
Occurrence of ADRs	ADRs during hospital stay	26 (26.3)
	ADRs at the time of admission	41 (41.4)
	Previous exposure of ADRs	11 (11.1)
	ADR as a reason for admission	21 (21.2)
Status of the reporter	Physician	80 (80.8)
	Clinical pharmacist	19 (19.2)

Abbreviations; ADRs: adverse drug reactions

Causality evaluation of the reported ADRs to HAART showed that 99 ADRs (67 hematological and 32 dermatological ADRs) were reported from 174 HIV-SPPs. Of the 99 ADRs, a higher number of ADRs were reported in males [70 (70.7%)] than in females [29 (29.3%)]. The highest number of ADRs were reported in the age group of 41–60 years (50.5%), followed by 21–40 years (43.4%), and then >60 years (6.1%). The CD4 T-cell count at the time of reporting ADRs was ≤350 cells/µl in 79 (79.8%) patients, followed by 350–500 cells/µl in 17 (17.2%) patients, and >500 cells/µl in three (3%) patients. The occurrence of ADRs was higher at the time of admission (41.4%), followed by hospital stay [26 (26.3%)] and during previous exposure of ADRs (11.1%). Furthermore, 21.2% of patients reported ADRs as the reason for their hospital admission. Most of the ADRs were reported by physicians (80.8%), followed by pharmacists (19.2%). The characteristics of reported ADRs are summarized in Table 2.

Of the 99 ADRs to HAART, 67 were hematological and 32 were dermatological. Higher number of hematological (76.1%) and dermatological (59.4%) ADRs were reported in males than in females (23.9% and 40.6%, respectively). Both hematological (53.7%) and dermatological (43.8) ADRs were higher in the age group of 41–60 years. The CD4 T-cell count was ≤350 cells/µl in both hematological (88.1%) and dermatological (62.6%) ADR groups. The highest number of hematological [40 (59.6%)] and dermatological [15 (46.8%)] ADRs were reported for the zidovudine + lamivudine + nevirapine-based HAART regimen, followed by the zidovudine + lamivudine + efavirenz based HAART regimen [16 (23.9%) and 6 (18.8%), respectively]. The characteristics of hematological and dermatological ADRs to HAART are shown in Table 3.

Of the 99 ADRs to HAART, the management approach was "drug withdrawal" for 56 (83.6%) hematological and 27 (84.4%) dermatological ADRs, followed by "no change in ADR management" for 10 (14.9%) hematological and 5 (15.6%) dermatological ADRs. Specific treatment was administered for 31 (46.3%) hematological ADRs, whereas symptomatic treatment was prescribed for 16 (50%) dermatological ADRs. The treatment outcome in both groups "recovered" after the suspected drug was withdrawn. A definite improvement was observed in patients with hematological (83.6%) and dermatological (81.3%) ADRs after "dechallenge." In 94% of hematological and 96.9% of dermatological ADRs, "no rechallenge" was documented. Three cases of hematological ADRs were subjected to rechallenge, one of which reported symptom recurrence and two reported no occurrence of ADR symptoms. As per the Naranjo probability scale, most of the hematological (61.2%) and dermatological (40.6%) ADRs to HAART were "probable" followed by "possible." WHO causality assessment was "probable" in 46 (68.7%) hematological and 20 (62.5%) dermatological ADRs. The severity of ADRs was "moderate" (i.e., level 3, 4a, or 4b) in 51 (76.1%) hematological and 22 (68.8%) dermatological ADRs, followed by "mild" (i.e., level 1 or 2) in 15 (22.4%) hematological and 9 (28.1%) dermatological ADRs, and "fatal" (i.e., level 5, 6, or 7) in one hematological and one dermatological ADR. Most of the serious ADRs [77 (85.1%) hematological and 29 (90.6%) dermatological ADRs] were reported during hospitalization. Majority of the reported ADRs in both groups were "predictable" and "definitely preventable." The

Table 3. Characteristic of hematological and dermatological ADRs

Characteristic		Number of hematological ADRs n = 67 (%)	Number of dermatological ADRs n = 32 (%)
Gender	Male	51 (76.1)	19 (59.4)
	Female	16 (23.9)	13 (40.6)
Age (years)	21–40	29 (43.3)	14 (43.7)
	41–60	36 (53.7)	14 (43.8)
	>60	2 (3.0)	4 (12.5)
Baseline CD4 count (cells/µl)	≤350	59 (88.1)	20 (62.6)
	350–500	8 (11.9)	9 (28.1)
	>500	*	3 (9.3)
HAART regimen			
Zidovudine + Lamivudine + Nevirapine		40 (59.6)	15 (46.8)
Zidovudine + Lamivudine + Efavirenz		16 (23.9)	6 (18.8)
Stavudine + Lamivudine + Nevirapine		3 (4.5)	6 (18.8)
Stavudine + Lamivudine + Efavirenz		2 (3.0)	2 (6.3)
Tenofovir + Emtricitabine + Efavirenz		1 (1.5)	3 (9.3)
Tenofovir + Lamivudine + Efavirenz		5 (7.5)	*

*No ADR reported
Abbreviations;
ADRs: adverse drug reactions, HAART: highly active antiretroviral therapy

assessment of hematological and dermatological ADRs to HAART is summarized in Table 4. With regard to the pattern of OIs, tuberculosis was reported in 77 (44%) patients, followed by candidiasis in 53 (30.4%) patients, pneumonia in 22 (12.6%) patients, and toxoplasmosis in 12 (6.9%) patients (Figure 3).

Of the 99 ADRs, most hematological ADRs were associated with the use of zidovudine, stavudine, and lamivudine.

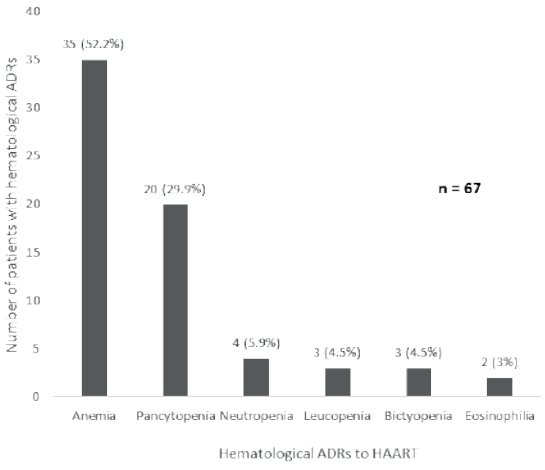

Figure 1. Pattern of hematological ADRs to HAART. (Abbreviations; ADRs: adverse drug reactions, HAART: highly active antiretroviral therapy)

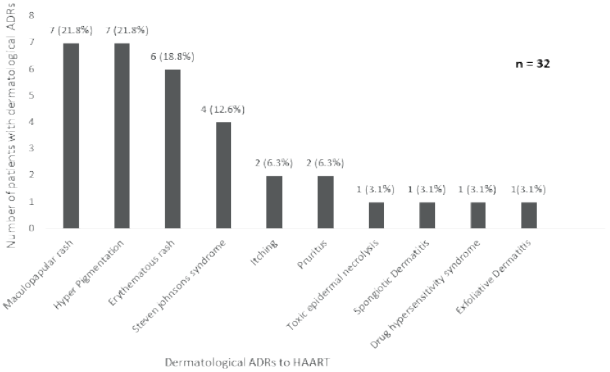

Figure 2. Pattern of dermatological ADRs to HAART. (Abbreviations; ADRs: adverse drug reactions, HAART: highly active antiretroviral therapy)

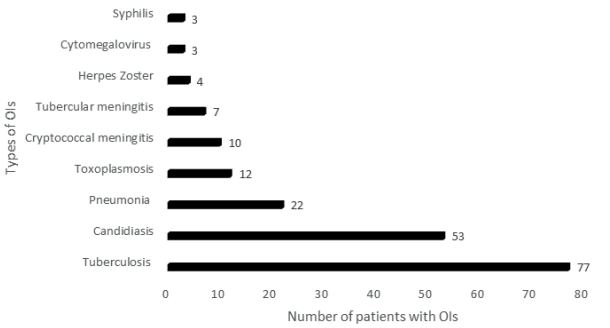

Figure 3. Pattern of OIs (Abbreviations; OIs: opportunistic infections)

Table 4. Assessment of hematological and dermatological ADRs

Assessment of ADRs		Number of hematological ADRs n = 67 (%)	Number of dermatological ADRs n = 32 (%)	Total number of ADRs n = 99 (%)
Management of ADRs	Drug withdrawn	56 (83.6)	27 (84.4)	83 (83.8)
	Dose altered	1 (1.5)	*	1 (1)
	No change	10 (14.9)	5 (15.6)	15 (15.2)
Treatment administered for the ADRs	Specific	31 (46.3)	8 (25)	39 (39.4)
	Symptomatic	10 (14.9)	16 (50)	26 (26.3)
	No change in the treatment	26 (38.8)	8 (25)	34 (34.3)
Treatment outcome of the ADRs to HAART	Recovery	60 (89.6)	31 (97)	91 (92)
	Continuing	3 (4.4)	1 (3)	4 (4)
	Unknown	4 (6)	*	4 (4)
Dechallenge status of the ADRs	No dechallenge	9 (13.4)	5 (15.6)	14 (14.1)
	Definite improvement	56 (83.6)	26 (81.3)	82 (82.8)
	No improvement	1 (1.5)	*	1 (1)
	Unknown	1 (1.5)	1 (3.1)	2 (2.1)
Rechallenge status of the ADRs	No rechallenge	63 (94)	31 (96.9)	94 (95)
	Recurrence of symptoms	1 (1.5)	*	1 (1)
	No occurrence of symptoms	2 (3)	1 (3.1)	3 (3)
	Unknown	1 (1.5)	*	1 (1)
Naranjo probability scale	Definite	2 (3)	*	2 (2)
	Probable	41 (61.2)	13 (40.6)	54 (54.6)
	Possible	24 (35.8)	19 (59.4)	43 (43.4)
WHO probability scale	Certain	3 (4.5)	*	3 (3)
	Probable	46 (68.7)	20 (62.5)	66 (66.7)
	Possible	18 (26.8)	8 (25)	26 (26.3)
	Unaccessable/Unclassifiable	*	4 (12.5)	4 (4)
ADR severity	Mild (Level 1 or 2)	15 (22.4)	9 (28.1)	24 (24.2)
	Moderate (Level 3, 4a, or 4b)	51 (76.1)	22 (68.8)	73 (73.7)
	Severe (Level 5, 6, or 7)	1 (1.5)	1 (3.1)	2 (2.1)
ADR seriousness	Hospitalization	57 (85.1)	29 (90.6)	86 (86.9)
	No hospitalization	10 (14.9)	3 (9.4)	13 (13.1)
ADR predictability	Predictable	67 (100)	24 (75)	91 (91.9)
	Not predictable	*	8 (25)	8 (8.1)
ADR preventability	Definitely preventable	26 (38.8)	14 (43.7)	40 (40.4)
	Probably preventable	20 (29.9)	4 (12.5)	24 (24.2)
	Not preventable	21 (31.3)	14 (43.8)	35 (35.4)

* Not reported
Abbreviations;
ADRs: adverse drug reactions, HAART: highly active antiretroviral therapy

The occurrence of hematological ADRs is summarized in Table 5: 1) anemia with zidovudine and stavudine [35 (52.2%)]; 2) pancytopenia with zidovudine [20 (29.9%)]; 3) neutropenia (5.9%) with lamivudine; 4) leucopenia (4.5%), bicytopenia (4.5%), and eosinophilia (3%) with zidovudine. The dermatological ADR of maculopapular rash [7 (21.8%)] was reported with the nevirapine-, tenofovir + emtricitabine + efavirenz-, and lamivudine-based HAART regimen, while hyperpigmentation [7 (21.8%)] was reported with the zidovudine-, nevirapine-, and lamivudine + emtricitabine-based HAART regimen. The patterns of hematological and dermatological ADRs to HAART are shown in Figures 1 and 2, respectively.

Table 5. Characteristics of ADRs to HAART

ADRs	Number of ADRs	Suspected antiretroviral medication
Hematological ADRs	n = 67 (%)	
Anemia	35 (52.2)	Zidovudine
Pancytopenia	20 (29.9)	Zidovudine
Neutropenia	4 (5.9)	Lamivudine
Leucopenia	3 (4.5)	Zidovudine
Bicytopenia	3 (4.5)	Zidovudine
Eosinophilia	2 (3)	Zidovudine
Dermatological ADRs	n = 32 (%)	
Maculopapular Rash	7 (21.8)	Nevirapine, Tenofovir + Emtricitabine + Efavirenz, Lamivudine
Hyperpigmentation	7 (21.8)	Zidovudine, Nevirapine, Lamivudine + Emtricitabine
Erythematous rash	6 (18.8)	Nevirapine, Efavirenz
Steven–Johnson syndrome	4 (12.6)	Nevirapine
Itching	2 (6.3)	Zidovudine
Pruritus	2 (6.3)	Zidovudine
Toxic epidermal necrolysis	1 (3.1)	Nevirapine
Spongiotic dermatitis	1 (3.1)	Emtricitabine
Drug-induced hypersensitivity syndrome	1 (3.1)	Efavirenz
Exfoliative dermatitis	1 (3.1)	Emtricitabine

Abbreviations;
ADRs: adverse drug reactions, HAART: highly active antiretroviral therapy

DISCUSSION

Various pharmacovigilance studies worldwide have reported that hematological and dermatological ADRs to HAART predominantly occur in females (1, 21-23). In contrast, our study showed the predominance of hematological and dermatological ADRs in males (70.7%) than in females (29.3%). These ADRs increase the length of hospitalization, causing repeat hospital admissions and additional financial burden on male patients. This finding indicates the gender difference in the occurrence of hematological and dermatological ADRs to HAART is consistent with the study conducted by Ighovwerha et al. (24) Other reasons for male predominance in our study could be the lower number of female HIV-SPPs compared with male HIV-SPPs. We found that due to social stigma associated with dermatological ADRs such as hyperpigmentation and maculopapular rashes, female HIV-SPPs do not adhere to the HAART routine, leading to treatment failure. This finding is consistent with the results of previous studies (25-28). However, in one study, a higher prevalence of ADRs to HAART was found due to switch over of HAART regimen prescription during follow-up than due to nonadherence to HAART (29). In our study, majority of the patients with hematological (53.7%) and dermatological (43.8%) ADRs to HAART were 41–60 years old; this is consistent with the findings of other

studies (9,30). This predominance was probably because a higher number of patients of this age group [87 (50%)] were admitted for HIV disease treatment during the study period. However, other studies (31-33) have reported a higher percentage of ADRs to HAART in geriatric and pediatric HIV-carrying populations.

In our study, HIV-SPPs with hematological and dermatological ADRs, such as toxic epidermal necrolysis with drug hypersensitivity syndrome, showed low CD4+ T-cell counts of ≤350 cells/µl, indicating that low CD4+ T-cell counts are a risk factor for hematological and dermatological ADRs to HAART in PLW-HIV. This finding is consistent with that of the study by Syed IA et al. who demonstrated that HIV patients with low CD4 T-cell counts had 2.28-fold (95% CI: 1.25–4.18) higher risk of developing ADRs (34).

The majority of hematological (59.6%) and dermatological (46.8%) ADRs to HAART, such as anemia, maculopapular rash, and hyperpigmentation, were due to zidovudine + lamivudine + nevirapine-based HAART regimen. In our study, this HAART regimen was switched to tenofovir + emtricitabine + efavirenz when patients developed virologic failure with the previous regimen. We observed an increase in CD4 T-cell counts after follow-up of 3 months with tenofovir + emtricitabine + efavirenz-based HAART regimen, in addition to a reduction in lamivudine-induced rash. The NACO guidelines (15) do not recommend the use of emtricitabine; however, our hospital widely prescribes emtricitabine-based regimen. The above finding is consistent with that of a case series by Sachdeva RK et al., wherein 23 patients developed lamivudine-induced rash (35).

During this study, nevirapine induced severe skin reactions, such as erythematous rash, in six cases (18.8%), Steven Johnson Syndrome (SJS) in four cases (12.6%), and toxic epidermal necrolysis (TEN) in one case. This finding is similar to the findings of Stewart A et al. (36) In our study, erythematous rash was moderate in severity and occurred within 4 weeks of nevirapine-based HAART regimen. The suspected drug nevirapine was then withdrawn, and symptomatic treatment was initiated. SJS (grade IV rash) was documented within 3 months of nevirapine use. The study by Carr DF et al. demonstrated the association of CYP2B6 c.983T>C polymorphism with nevirapine-induced hypersensitivity reactions in HIV-SPPs in Malawi and Uganda. However, no such association with nevirapine-induced SJS was found in Caucasians (37). These findings indicate that the possibility of ethnic predisposing factor for nevirapine-induced hypersensitivity reactions. However, we did not perform genome study to identify such associations with nevirapine-induced SJS or TEN. In our study, one death occurred due to nevirapine-induced TEN. This finding is consistent with the results of previous studies wherein nevirapine-induced TEN resulted in life-threatening ADRs (38,39).

Exfoliative dermatitis (ED), characterized by skin scaling and red and inflamed blisters, was observed in one patient receiving emtricitabine-based HAART regimen. On withdrawing emtricitabine, the adverse symptoms of the patient gradually resolved after 2 months. This finding of emtricitabine-induced ED was a rare dermatological ADR observed in our hospital. In a similar study, Zhang et al. reported efavirenz-induced ED with fever, blistering, and desquamation (40). Munyao et al. reported ED in 14% of HIV/AIDS patients with tuberculosis in Nairobi and adjacent districts accompanied with a low mortality rate (41). Salami et al. reported that ED is associated with malignancies in elderly patients (42).

In our study, drug-induced hypersensitivity syndrome (DIHS), characterized by urticarial rash and skin ulceration, was observed with the efavirenz-based HAART regimen in one patient. The patients showed recovery from DIHS after 4 weeks of efavirenz discontinuation. In a recent study, Eyer-Silva et al. reported DIHS after initiating darunavir and raltegravir in a patient who presented with cutaneous eruption on the face, a rash suggestive of DIHS with facial edema, mainly periorbital with follicular accentuation (43) similar results have been reported in studies on the risk of abacavir-induced DIHS (44,45) In our study, one patient showed emtricitabine induced spongiotic dermatitis characterized by severe pruritis followed by skin lesions on the trunk, commonly termed as drug-induced immune reconstitution syndrome. This finding was consistent with that of the study by Krucke et al. (46).

In our study, most of the hematological ADRs were associated with the zidovudine + stavudine and lamivudine-based HAART combination regimens, which is consistent with other studies that reported a higher incidence of hematological ADRs with zidovudine + lamivudine + efavirenz HAART regimen (47-49). Notably, hematological ADRs of anemia (52.2%), pancytopenia (29.9%), neutropenia (5.9), leucopenia, bicytopenia, and eosinophilia were reported in patients with advanced HIV disease in our study.

To avoid zidovudine induced-anemia, physicians at our hospital prescribe zidovudine-based HAART only when hemoglobin levels are >8 g/dl at baseline. Although a higher incidence of zidovudine-induced anemia, was reported. ADRs associated with zidovudine-induced anemia was easily predicted with routine follow-up of hemoglobin levels and complete blood count. Our study showed were common (incidence ≥1/100 and <1/10) or very common (incidence ≥ 1/10), similar to that in the study by Mehta et al. (30). However, in our study, preventive measures of switching to non-zidovudine-based HAART, blood transfusion, and human erythropoietin were recommended. In a recent study, Woldeamanuel GG et al. compared the prevalence of anemia before and after the initiation of antiretroviral therapy in HIV-SPPs and reported that screening and treatment to avoid hematological abnormalities related to antiretroviral therapies are crucial to reduce the prevalence of anemia (50). In India, several studies have consistently reported a higher incidence of zidovudine-induced anemia (3,9,51-53). However, other studies from developed countries have reported a low incidence of anemia in patients exclusively on a zidovudine-based HAART regimen (29). The main limitation of this study was low power due to a short study

period and limited number of patients.

CONCLUSION

In this study, we found a higher incidence of hematological ADRs to HAART than of dermatological ADRs, although one death occurred because of SJS, a dermatological ADR to HAART. Our findings suggest that most of the hematological and dermatological ADRs are preventable by screening for early signs during follow-ups. Therefore, in India, treating physicians show focus on early detection, prevention, and management of ADRs to HAART in PLW-HIV.

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AUTHOR CONTRIBUTIONS

All authors are equally contributed for the conduct of this study. First Author and corresponding authors designed the methods, while Third author conducted the study under the supervision of Fourth author in Medicine department of the study hospital. Fifth author helped us with statistical analysis.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

ETHICAL STANDARDS

Ethical standards were obtained for the conduction of this study as per the Institutional Ethical Clarence approval.

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