Original Article

Clinicoepidemiological study of adverse cutaneous drug reactions among immunocompromised children at a tertiary care hospital

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Abstract

Introduction: Highly active antiretroviral therapy (HAART) is used to treat human immunodeficiency virus type 1 (HIV-1). Introduction of antiretroviral therapy (ART) has reduced the HIV/AIDS associated morbidity and mortality significantly. But 25% of all patients discontinue treatment because of adverse drug reactions (ADRs). Adverse cutaneous drug reactions (ACDR) are very common with ART regimens, which may range from mild pruritus, maculopapular rash to serious Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). ACDRs comprise 10%–30% of all reported ADRs. **Aims and Objectives:** To assess the different types of cutaneous adverse drug reactions in immunocompromised children of less than 18years. **Materials and Methods:** This is a retrospective record-based study, conducted at department of Dermatology, Venereology and Leprosy, Government Medical College (GMC)/Government General Hospital (GGH), Suryapet, Telangana, India. Data was collected from the records available at ART centre, from November 2018 to October 2021 GGH, Suryapet. All the HIV infected children ≤18 years who were on ART, were included in this study. Patients of more than 18 years and on other medications were excluded. Demographic data, socio economic status, vaccination status, height, weight, complete blood analysis, complete urine analysis, erythrocyte sedimentation rate, liver and renal function tests and CD4 counts were recorded before initiation of ART. **Results:** A total of 330 children of less than 18 years were initiated for ART, at ART centre, Government General Hospital, Suraypet. Out of 330 children, 27.8% (92) children developed ACDRs. 58.7% (54) were males and 41.3% (38) were females. Maculopapular rash was seen in 65.2% (60) cases, urticaria was seen in 15.3% (14) cases, Steven Johnson Syndrome (SJS) was seen in 9.8% (9) cases, SJS/TEN overlap was seen in 6.5% (6) cases and toxic epidermal necrolysis (TEN) was seen in 3.2% (3) case. CD4 count was below 300 in 65.3% (60) cases above 300 in 34.7% (32) cases. Gap between initiation of the treatment and onset of reaction was less than one month in 65.3% (60) cases, and more than one month in 34.7% (32) cases.

Key words: Adverse cutaneous drug reactions, antiretroviral therapy, children, human immunodeficiency virus, immunocompromised

Introduction

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), there are approximately 37.7 million people across the globe who were found to be affected by human immunodeficiency virus (HIV) as of 2020. Of these, 36 million were adults and 1.7 million were children aged 0–14 years. More than half (53%) of them were female.[1] Highly Active Antiretroviral Therapy (HAART) is used to manage and treat HIV type 1. Antiretroviral (ARV) drugs are not a cure for HIV, but they reduce mortality and morbidity and help improve the quality of life of HIV patients.

Anti - retroviral Therapy (ART) is a double-edged sword with its positive effects at one end and its potential life-threatening and morbid side effects on the other. In children, compliance is a major issue. ART in children

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consists of three groups of drugs, the nucleoside reverse transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs), and the protease inhibitors (PIs). Triple-drug therapy is used to suppress viral replication and arrest the progression of HIV disease.[2] However, 25% of all patients discontinue their initial HAART regimen because of adverse drug reactions (ADRs).[3]

ADR is a response to a medicine that is noxious and unintended and which occurs at doses normally used in humans for diagnosis, prevention, and treatment. The incidence of adverse reaction is 1 in 10,000.[4] Adverse cutaneous drug reactions (ACDRs) are very common with ART regimens, which may range from mild reactions such as pruritus, maculopapular rash, fixed drug eruption, erythema multiforme to severe forms such as Steven–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug hypersensitivity syndrome.[5] ACDRs comprise 10%–30% of all reported ADRs.[6-8]

Fixed-dose combination (FDC) of Tenofovir 300 mg + Lamivudine 300 mg + Dolutegravir 50 mg (TLD) regimen is the preferred first-line regimen for initiation of ART on naive HIV cases. As per the World Health Organization guidelines, people living with HIV above 6 years of age and weighing more than 20 kg are eligible for dolutegravir (DTG)-based regimens.[9] Children on the adult dosage of Zidovudine, Lamivudine, and Nevirapine (ZLN) are transitioned to DTG-based regimen.

An appropriate ART regimen was initiated in children regardless of the WHO clinical staging or immune staging.[2] The choice of ARV drugs depend on the child's age, weight, and the presence or absence of anemia (Hb: <9 g/dl). For anemic children, iron supplementation was given. In children with HIV infection, zidovudine (AZT) is the preferred NRTI for initiation. If the child is found to have anemia, abacavir is considered the drug of choice for initiation. In children above 10 years and above 30 kg body weight, tenofovir is the preferred drug for initiation. Stavudine has been phased out from the pediatric first-line regimen; however, it is used in case of dual toxicity both for zidovudine and abacavir. The use of stavudine may be considered an alternative in children below 10 years of age and having a body weight of <30 kg. Lopinavir/ritonavir (LPV/r) is recommended as the preferred third drug in all children <3 years of age. For children older than 3 years, efavirenz (EFV) is the preferred third drug[2] [Figure 1].

Dolutegravir (DTG) has been introduced in the ART regimen in 2020. Raltegravir is replaced by Dolutegravir from 28-05-2020, and Zidovudine + Lamivudine + Nevirapine regimen is replaced with the Dolutegravir -based regimen from 07-07-2020 by NACO (National Aids Control Organization). Dolutegravir is an integrase inhibitor. DTG is a single drug used in combination with other Anti - Retroviral drugs. According to the Technical Open access Epi info version Resource Group recommendations, a DTG-based regimen (TLD) is recommended as a first-line drug for ART initiation under the national program and various combinations of DTG are recommended as an alternative first-line, second-line, and third-line regimen [Figure 1].[10]

Aims and objectives

To study the diverse types of cutaneous ADRs, among immunocompromised children under 18 years of age.

Methodology

A retrospective record-based study was conducted at the Department of Dermatology, Venereology and Leprology, Government Medical College/Government General Hospital, Suryapet, Telangana, India.

Study design

Retrospective record-based study.

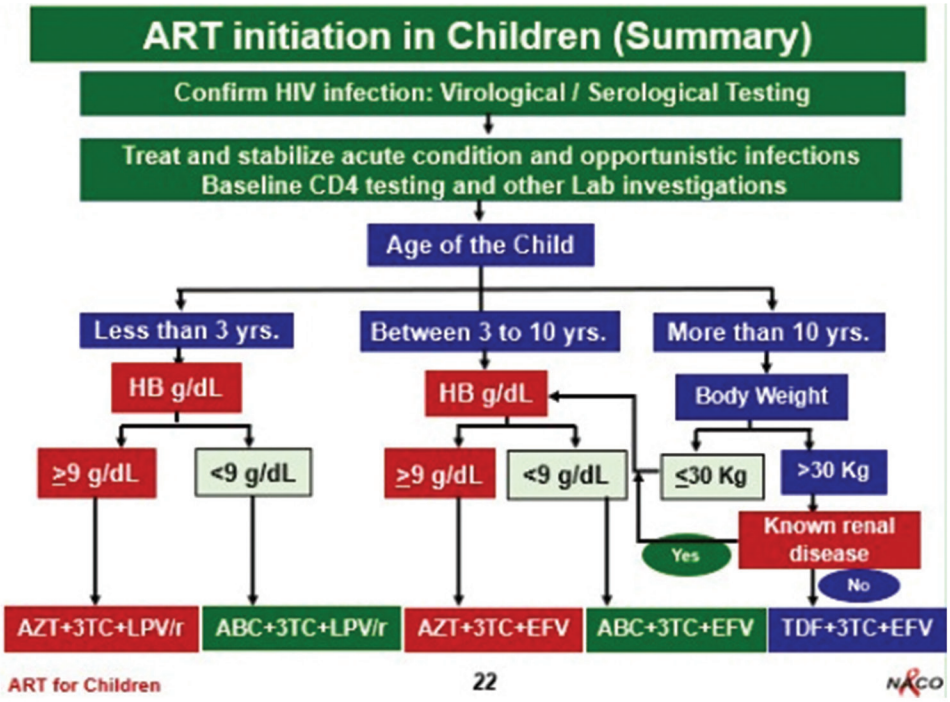

Figure 1: Chart showing ART initiation in children

Study population
Children of below 18 years of age, who were on ART Regime.

Study setting
Government General Hospital/Government Medical College, Suryapet.

Sample size
Considering the prevalence of cutaneous ADR among children with ART, i.e., 17.4%,[11] an absolute error of l = 5% sample size of n = 230 was achieved; however, the data were collected from 330 available records.

Study period
Three months (data were collected from hospital records which were maintained for a period of 3 years, starting 2018 till 2021).

Study variable
Cutaneous ADR among children on ART regimen.

Table 1: Age and sex distribution

Age group (years)	Males, *n* (%)	Females, *n* (%)	Total, *n* (%)	*P*
0-6	9 (2.7)	7 (2.2)	16 (4.9)	0.28
7-12	22 (6.6)	25 (7.6)	47 (14.2)	
13-18	158 (47.9)	109 (33)	267 (80.9)	
Total	189 (57.2)	141 (42.8)	330 (100)	

Table 2: Age and sex distribution of adverse cutaneous drug reactions

Age (years)	Males, *n* (%)	Females, *n* (%)	Total, *n* (%)	*P*
0-6	3 (3.2)	1 (1.1)	4 (4.3)	0.78
7-12	13 (14.2)	9 (9.8)	22 (24)	
13-18	38 (41.3)	28 (30.4)	66 (71.7)	
Total	54 (58.7)	38 (41.3)	92 (100)	

Inclusion criteria
All the HIV-infected children under 18 years of age on ART were included in the study.

Exclusion criteria
Patients more than 18 years and children on other medications were excluded from the study.

The data were collected from the hospital-based records maintained at the Medical Record Department unit. The data were analyzed using Microsoft Excel version 2010, Open access Epi info version 3.30, (statistical software for epidemiology developed by Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia (US)),by applying a Chi-square test for the level of significance to cross-tables, and mean and standard deviation were calculated for continuous variables such as age.

Observation and Results
A total of 330 children below 18 years were initiated on ART. The mean age and standard deviation of the total study population were 14.2 ± 3.65 years. Out of 330 cases, 92 (27.8%) children developed ACDRs aged 13.8 + 3.74 years. Among them, 54 (58.7%) were male and 38 (41.3%) were female. Most of the ACDRs were observed between 13 and 18 years of age (71.7%, 66), followed by 7–10 years' age group (24%, 22). (*P* value >0.05, which is not significant). Thus, the selection of the subjects was homogenous with respect to age and gender [Tables 1 and 2]. ART regimen was initiated according to the NACO guidelines. Different types of regimens were given according to age, weight, and hemoglobin levels. Tenofovir + lamivudine + EFV (TLE) was given to 140 (42.4%) children, and tenofovir + lamivudine + DTG (TLD) to 79 (23.9%) children. Different types of regimens and ACDRs observed with ART regimens are shown in Table 3.

Maculopapular rash [Figure 2] was observed in 60 (65.4%) cases, urticaria in 14 (15.4%), SJS [Figure 3] in 9 (9.6%),

Table 3: Different antiretroviral therapy regimen and associated adverse cutaneous drug reactions

Drug regimen	0-6 years, *n* (%)	7-12 years, *n* (%)	13-18 years, *n* (%)	Total, *n* (%)	ACDRs, *n* (%)
Zidovudine + lamivudine+efavirenz	7 (2.1)	19 (5.8)	1 (0.3)	27 (8.2)	U=3 (3.2) MPR=6 (6.5)
Abacavir + lamivudine+nevirapine	6 (1.8)	7 (2.1)	10 (3.0)	23 (6.9)	U=4 (4.4) MPR=8 (8.7) SJS=3 (3.2) SJS/TEN=2 (2.1) TEN=1 (1.1)
Zidovudine + lamivudine+nevirapine	0	5 (1.5)	14 (4.3)	19 (5.8)	U=1 (1.1) MPR=5 (5.5) SJS=3 (3.2) SJS/TEN=2 (2.1) TEN=1 (1.1)
Zidovudine + lamivudine + lopinavir/ritonavir	0	6 (1.8)	0	6 (1.8)	Nil
Tenofovir + lamivudine + efavirenz	0	9 (2.7)	131 (39.7)	140 (42.5)	U=6 (6.7) MPR=28 (30.5) SJS=3 (3.2) SJS/TEN=2 (2.1) TEN=1 (1.1)
Tenofovir + lamivudine+lopinavir/ritonavir	0	0	3 (0.9)	3 (0.9)	Nil
Tenofovir + lamivudine+dolutegravir	0	0	79 (23.9)	79 (23.9)	MPR=9 (9.9)
Abacavir + lamivudine+dolutegravir	2 (0.6)	0	14 (4.3)	16 (4.9)	MPR=4 (4.3)
ZLD	1 (0.3)	1 (0.3)	9 (2.8)	11 (3.3)	Nil
AL + LPV/R + D	0	0	2 (0.6)	2 (0.6)	Nil
LPV/R + D	0	0	4 (1.2)	4 (1.2)	Nil
Total	16 (4.8)	47 (14.2)	267 (81)	330 (100)	92 (100)

ACDRs=Adverse cutaneous drug reactions; U=Urticaria; MPR=Maculopapular rash; SJS=Steven-Johnson syndrome; TEN=Toxic epidermal necrolysis; LPV/R+D=Lopinavir/ritonavir + dolutegravir; AL + LPV/R+D=Abacavir + lamivudine+LPV/R + D; ZLD=Zidovudine + lamivudine + dolutegravir

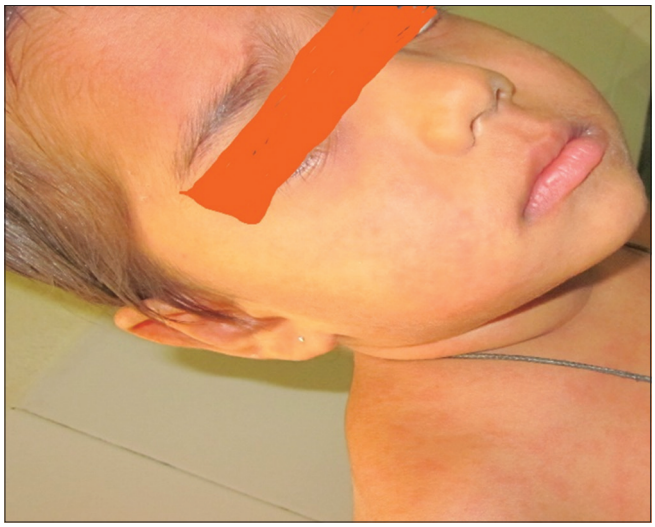

Figure 2: Developed maculopapular rash after 12 days of ART therapy in a child.

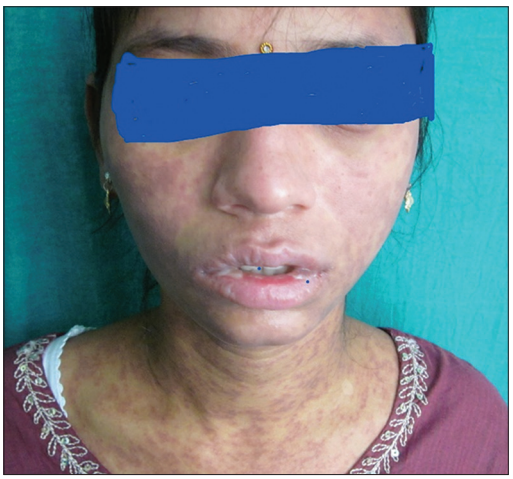

Figure 3: Steven–Johnson syndrome in an adolescent girl, developed 2 weeks after ART therapy

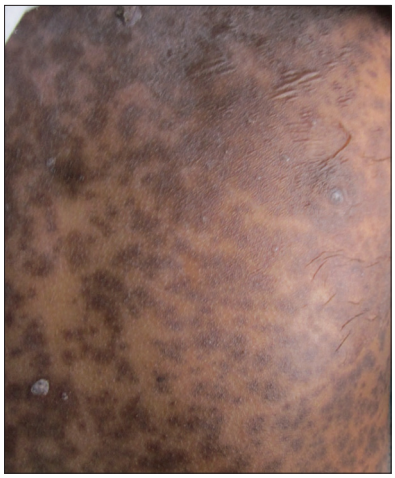

Figure 4: Developed toxic epidermal necrolysis (positive Nikolsky sign, skin tenderness) 20 days after ART therapy in an adolescent child

SJS/TEN overlap in 6 (6.3%), and TEN [Figure 4] in 3 (3.3%) cases. Grade II reactions were seen in 65.2% of cases, followed by Grade I reactions in 15.3%, Grade III reactions in 16.3%, and Grade IV reactions in 3.2%.

Table 4: CD4 count

CD4 count	Number of cases without ACDRs, *n* (%)	Number of cases of ACDRs, *n* (%)	Total	χ^2, *P*, df
<100	11 (3.3)	13 (3.9)	24 (7.2)	11.33, 0.02, 4
101-200	34 (10.3)	15 (4.5)	49 (14.8)	
201-300	78 (23.6)	32 (9.7)	110 (33.3)	
301-400	54 (16.4)	14 (4.3)	68 (20.7)	
>400	61 (18.6)	18 (5.4)	79 (24)	
Total	238 (72.2)	92 (27.8)	330 (100)	

ACDRs=Adverse cutaneous drug reactions

In 34.8% (32) cases, CD4 count was between 201 and 300, CD4 count was more than 400 in 19.6% cases, 101–200 in 16.3% of cases, 301–400 in 15.2% of cases, and <100 in 14.1% of cases. (P value significant at 0.02 was calculated with respect to ACDRs common among individuals having 201–300 cell/ml count) [Table 4].

ACDRs were observed after 4 weeks of initiation of therapy in 32 (34.7%) cases, <1 week in 25 (27.2%) cases, 3rd week in 15 (16.3%) cases, and 2nd week in 12 (13.1%) cases.

In our study, ACDRs were observed in 78.2% of children on ALN regimen, 63.15% on ZLN regimen, and 28.6% on TLE regimen. ZL + LPV/R, TL + LPV/R, ALD + LPV/R, LPV/R + D, and ALD were relatively safer regimens as there were no recorded ACDRs seen with these regimens. SJS, SJS/TEN, and TEN cases were seen more with the nevirapine-based regimen (13.04% cases) followed by EFV-based regimen 6 (6.52%) cases [Figure 1 and Table 3].

Discussion

There is an impression that children are at a lower risk of ADRs than adults. This finding may be due to the majority of the studies having been conducted among adults. However, there is an increasing number of studies demonstrating that children also have an appreciable risk for ADRs. The risk for ADRs in children may be attributed partly due to known risk factors and partly due to the nature of pharmacotherapy for children.[12] Children are more susceptible than adults to drug reactions because of their smaller body size,[13] the level of maturity of body systems involved in absorption, metabolism, transportation, and elimination of drugs. The known risk factors for ADRs in children are the history of a previous ADR, extremes of age, impaired renal or liver function, polypharmacy, female sex, genetic polymorphisms, general anesthetic use, use of off-label drugs, slow acetylator status, relative glutathione deficiency, and CD4 count of <200/mm^3 or more than 25 cells/mm^3.[12,14,15] Up to 80% of HIV-infected patients developed ADRs at some point of therapy; this could be due to immune dysregulation, altered drug metabolism, and polypharmacy.[16] They have a higher risk of developing cutaneous reactions than the general population. A thorough knowledge of clinical presentation of ACDRs is essential for establishing the diagnosis. A detailed history regarding the initiation of ART, onset of skin lesions, involvement of mucosa, constitutional symptoms, and previous history of similar reactions must be taken. For severe life-threatening reactions, appropriate investigations should be done.

In our study, out of 330 cases, 92 (27.9%) children developed ACDRs as compared to a study conducted by

Oumar *et al*., which showed 38.5% of ACDR in children with ART.[17] In Abdela *et al*.'s study, ACDRs were observed in 17.4% of the children on ART.[11] In Shah's study, it was 9%.[18] ACDRs comprise 10%–30% of all reported ADRs and its incidence in hospitalized patients is estimated to be 2%–3%.[19]

In our study, males (58.7%) were more affected than females (41.3%; M:F: 1.42:1), which was also seen in Oumar *et al*.'s study. However, in Abdela *et al*.'s study, female outnumbered males.

In our study, the most common age group involved is 13–18 years. In Oumar *et al*. study ADRs were seen more in 5–9 years of age group.[17] In Abdela *et al*.'s study, it was 11–15 years.[11] This finding may be because a greater number of HIV cases on ART was from this age group.

In 34.7% (32) of cases, ACDRs observed after 4 weeks of initiation of ART, less than one week 25 (27.2%) cases. Most of the ADRs (86%) occur within first 4–6 weeks of initiation of ART.[8,15]

CD4 count was more than 400 in 19.6% of cases, 101–200 in 16.3% of cases, 301–400 in 15.2% of cases and <100 in 14.1% of cases. Abdela *et al*. study CD4 count was more than 500 in 69.9% of cases. CD4 count below 200, was identified as a major risk factor which may predisposes patients to ADRs.[20] As the CD4 count declines and viral load increases, the risk of ADRs increases. Most of the reactions appear in patients with CD4 counts <100cells/μL.[21,22] The probable mechanisms of the increased sensitivity to ADRs may be immune related, because of low CD4 count, or infection-related, due to accumulation of HIV-specific factors.[21-23]

In our study, ACDRs occurred more with ALN regimen (78.2%-18/23), followed by ZLN regimen (63.15%) and TLE (28.6%). ZL + LPV/R, TL + LPV/R, ALD + LPV/R, LPV/R + D, and ALD were relatively safer regimens as there were no ACDRs with these regimens. SJS, SJS/TEN, and TEN cases were seen in 13.04% (12) of children on nevirapine-based regimen, followed by EFV based regimen 6 (6.52%) cases. ACDRs are common with all ARVs, but they are more with NNRTIs such as nevirapine and EFV.[24] Severe life-threatening adverse cutaneous reactions such as SJS, TEN, and hypersensitivity reactions occur most commonly with the NNRTIs (nevirapine and EFV), the NRTIs (abacavir), and the PIs (indinavir and amprenavir).

Limitations

This is a hospital-based study. Lack of awareness among parents might have led to underreporting of adverse events. Mild reactions might have been managed by pediatricians or quacks, hence were not reported to dermatologists. Clinical records were often incomplete, lacking important clinical details. It was difficult for follow-up of patients as they come from rural areas. Therefore, our study findings were interpreted in the context of these limitations.

Conclusion

Our study demonstrated that around 27% children on ART developed ACDRs. However, they experienced mild-to-moderate reaction of Grade I and Grade II severity. Nevirapine-based regimens were associated with severe reactions, hence replaced by DTG-based regimen. In pediatric HIV patients, appropriate ART regimen should be given to reduce ADRs, in specific cutaneous ADRs. FDC of ART may improve the adherence to therapy. There is a need for the invention of children friendly drugs with minimal side effects. Drugs that are cross-reactive have to be identified and avoided. High index of suspicion is required for early detection (bright erythematous rash associated with itching and with involvement of palms and soles) and treatment of cutaneous ADRs to ARV therapy to prevent progression and complications. Identification of the causative agent and its avoidance is essential to halt the progression of reaction. Avoiding cross-reactive drugs is also necessary to prevent ADRs. Constant pharmacovigilance will help in the detection, assessment, and prevention of ADRs. Literature on ACDRs with ART is mostly in the form of case reports and case series only; however, original studies available are limited in number. The present study includes a good number of cases and it stands as a guide for future research.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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