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Original Article

Pharmacology Section

Nevirapine: Most Common Cause of Cutaneous Adverse Drug Reactions in an Outpatient Department of a Tertiary Care Hospital

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ABSTRACT

Introduction: Skin is the most commonly involved organ in adverse drug reactions. Most of the cutaneous adverse drug reactions (CADRs) being of mild to moderate severity are likely to be diagnosed and treated in an outpatient setting. Consequently, knowledge regarding morphological pattern, severity and drugs implicated in causation of these CADRs has important implications for healthcare personnel.

Aim: To determine the current clinical pattern of CADRs and to assess their causality and severity with the help of standard scales.

Study design and setting: A prospective, observational study was conducted in the outpatient department of skin and venereal disease in a tertiary care hospital.

Materials and Methods: Patients with suspected CADR after consumption of systemic drug(s) were enrolled in the study. Data regarding demographics, clinical manifestations of CADR, drug history preceding the reaction, concomitant illness, relevant laboratory investigations etc was obtained. This data was then analysed for morphological pattern, causality and severity. CADRs with causality assessment possible and above on the basis of World Health Organization-Uppsala Monitoring Centre causality assessment system were considered for analysis.

Statistics: Descriptive statistics were used to express results of pattern, severity and causality of CADRs.

Results: Ninety patients were enrolled in the study. Male to female ratio for CADRs was 1:2.33. Maculopapular rash was most commonly encountered CADR in 76.67% cases followed by urticaria (8.89%), Stevens-Johnson syndrome (4.4%) and fixed dose eruptions (3.33%). Antiretrovirals were implicated in 75.56% (68/90) of CADRs. Nevirapine was suspected in 52 out of 90 (57.77%) cases of CADRs which included 39 cases of maculopapular rash, five cases of urticaria, four cases of Stevens-Johnson syndrome, and two cases each of pustular rash and angioedema respectively. Antimicrobials, antiepileptics and Non-steroidal Anti-inflammatory Drugs (NSAIDs) were other suspected drugs.

Conclusion: Antiretrovirals especially nevirapine was implicated in variety of CADRs ranging from maculopapular rash to life-threatening reactions like Stevens-Johnson syndrome in an outpatient setting. Women were twice as susceptible as men for CADRs.

Keywords: Antiretroviral agents, Drug eruptions, Drug toxicity

INTRODUCTION

All drugs carry the potential for causing injury through adverse effects even if used appropriately. Adverse drug reactions (ADRs) are an important cause of morbidity and mortality in hospital settings [1]. When overall pattern of ADRs is taken into account; cutaneous adverse drug reactions (CADRs) constitute the most common ADR type in hospital setting [2,3]. The incidence of CADRs in hospitalized patients ranges from 1-3% in developed countries (the frequency of these reactions to specific drugs may exceed 10%) [4]. The pooled incidence of CADRs is reported to be 9.22/1000 total among outpatient and inpatient cases in Indian population by a recent systematic review [5]. The incidence of CADRs in an outpatient setting is not well known, but a one year survey by Chatterjee et al., in dermatology outpatient setting showed that the incidence of CADRs in these patients was 2.66% [6].

The clinical spectrum of CADRs ranges from mild, self-limiting eruptions to severe life-threatening disease. Drug reactions may be confined solely to the skin or may have systemic involvement [7]. Fortunately, most CADRs are of mild to moderate severity and often resolve on withdrawal of an offending agent. Consequently, most of the CADRs are likely to be diagnosed and treated in an outpatient setting, making surveillance in an outpatient department essential. Moreover, with changing trends and emerging new therapies, the pattern of CADRs and drugs implicated in causation of these are bound to change. This is exemplified by higher incidence of CADRs in HIV-positive patients [8] or newer target therapies in cancer and drugs used in multidrug resistant tuberculosis causing CADRs [9-11]. Likewise, CADR pattern understandably varies in different regions owing to services provided and prescribing practices followed by the physicians.

Thus, CADRs 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. With this background, we undertook the present study with the aim of determining current clinical pattern of CADRs in our setting. We have also assessed causality and severity of these CADRs with the help of standard assessment systems.

MATERIALS AND METHODS

This prospective observational study was conducted in the outpatient department of skin and venereal disease in a tertiary care hospital from June 2013 to June 2014. The study was approved by ethics committee of the institute to which this hospital is attached.

Patient Inclusion Criteria

All patients irrespective of age and gender presenting to dermatology outpatient department with suspected CADR after systemic drug consumption and who were willing to give informed consent were enrolled in the study. ADR was defined as, "A response to a drug

which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function" [12].

Patient Exclusion Criteria

The patients in whom proper drug history could not be elicited due to problems such as inability to recall names of medicines consumed, language barrier etc. were not involved in the study. Patients in whom cutaneous manifestations were suspected to be due to use of topical medications or indigenous (homeopathic, ayurvedic etc.) medications and patients who declined to participate were also excluded from the study.

Data collection

The patients satisfying inclusion and exclusion criteria were enrolled in the study. Detailed clinical history, drug history and relevant information like onset of the reaction, it's duration and temporal association with drug intake if any, enlistment of all drugs taken preceding the onset of reaction, past history of drug rashes, reports of relevant laboratory investigations undertaken to arrive at a clinical diagnosis etc. was recorded in a pre-designed case record form.

Assessment of pattern, causality and severity

For knowing pattern, CADRs were categorized into various morphological types such as maculopapular rash, urticaria, fixed dose eruption etc. The diagnosis of CADR was made by a dermatologist. Various CADRs were defined according to standard reference [13]. Maculopapular (MP) rash was graded from grade 1-3 as per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [14]. According to this criteria, Grade1 MP rash is defined as macules/papules covering <10% Body Surface Area (BSA) with or without symptoms (e.g., pruritus, burning, tightness), Grade2 MP rash as macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness etc.); limiting instrumental Activities of Daily Living (ADL) and Grade3 MP rash as macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADL.

Causality assessment of CADRs was done on the basis of World Health Organization-Uppsala Monitoring Centre causality assessment system [15]. CADRs with causality assessment possible and above were included in the final analysis. Severity of CADRs was assessed by modified Hartwig and Siegel scale [16].

STATISTICAL ANALYSIS

The data was entered in the excel sheet. Demographic data was expressed as percentage or mean ±SD. Descriptive statistics was used to express the results regarding pattern, severity and causality assessment of the ADRs.

RESULTS

Demographic characteristics of study population are shown in [Table/Fig-1]. Seventy percent patients experiencing CADR belonged to female gender. About 68% of patients fell in the age group of 21-40 years. The clinical pattern of CADRs is shown in [Table/Fig-2]. MP rash was predominant pattern of CADRs and occurred in 76.67% of cases. Most of these patients (66.67%) exhibited Grade 3 MP rash. Urticaria was next common finding that occurred in 8.89% of patients. Steven-Johnson Syndrome (SJS) occurred in 4.44% of cases. Pruritis accompanying CADR was seen in 46.67% (42/90) cases. All patients of SJS were hospitalized and treated successfully. Amongst the drug classes suspected to have caused CADRs [Table/Fig-3] antiretroviral agents were implicated in 75.56% of CADRs while antibacterial, antiepileptic and non-steroidal anti-inflammatory drugs (NSAIDs) were implicated in about 20% of CADRs. The individual drugs implicated in various CADRs with their frequency are shown in [Table/Fig-4]. As can be seen from this table, Nevirapine (NVP) was the suspected drug in 39 cases of MP rash, 5 cases of urticaria, 4 cases of SJS, 2 cases of pustular rash and 2 cases of angiodema and accounted for 57.78% (52/90) of CADRs. Causality assessment is shown in [Table/Fig-5]. Causality was probable in 57.78% and possible in remaining 42.22%. Severity assessment is shown in [Table/Fig-6]. On modified Hartwig and Siegel scale, 78.89% CADRs belonged to mild category, 16.67% to moderate category while 4.44% belonged to severe category.

DISCUSSION

The skin is most commonly involved organ in adverse drug reactions. Although few CADRs are potentially life threatening and cause significant morbidity and mortality, most CADRs have favourable course and generally resolve after discontinuation of the offending agent. Consequently, most of the patients with CADRs are likely to present and get treated in an outpatient setting, making prospective surveillance of CADRs in an outpatient setting essential.

Characteristics	Value*
Total number of patients	90
Age (Year) Mean+SD Range	 33.74+11.67 03-67
Gender Male Female	 27 (30%) 63 (70%)
Weight (Kg) Mean+SD Range	 46.58+9.81 10-68
Habits Alcohol Tobacco Smoking Alcohol + Smoking	 06 (6.67%) 05 (05.56%) 01 (01.11%) 03 (03.33%)

[Table/Fig-1]: Demographic and baseline characteristics of patients with CADRs (n=90)
*values are expressed as Mean+SD or %

Clinical type	Number of CADR	Percentage
Maculo-papular rash Grade 1 Grade 2 Grade 3	69 12 11 46	76.67 17.39 15.94 66.67
Urticaria	08	08.89
Stevens-Johnson Syndrome	04	04.44
Fixed Drug Eruption (FDE)	03	03.33
Pustular rash	02	02.22
Angioedema	02	02.22
Exfoliative dermatitis	02	02.22
Total	90	

[Table/Fig-2]: Clinical pattern of CADRs (n=90)

Drug Group	Maculo-papular rash (%)	Urticaria (%)	SJS (%)	FDE (%)	Pustular rash (%)	Angiodema (%)	Exfoliative Dermatitis (%)	Overall (%)
Antiretroviral	53(58.89)	07(07.78)	04(04.44)	-	02(02.22)	02(02.22)	-	68(75.56)
Antibacterial	08(08.89)	-	-	-	-	-	01(01.11)	09(10)
Antiepileptic	03(03.33)	-	-	02(02.22)	-	-	01(01.11)	06(06.67)
NSAIDs	02(02.22)	01(01.11)	-	01(01.11)	-	-	-	04(04.44)
Antihistaminics	01(01.11)	-	-	-	-	-	-	01(01.11)
Others	02(02.22)	-	-	-	-	-	-	02(02.22)

[Table/Fig-3]: Morphological types of CADRs and suspected drug classes with frequency (n=90)

Type of cutaneous reaction	Drugs implicated with frequency of occurrence	Total number of cases	Percentage of total cases
Maculo-papularrash	nevirapine(39), efavirenz(10), zidovudine(02), lamivudine(02), azithromycin(02), roxithromycin(01), ciprofloxacin(01), cotrimoxazole(01), cotrimoxazole + levofloxacin(02), dapsone(01), phenytoin(03), finasteride(02), diclofenac(02), cetirizine(01)	69	76.67
Urticaria	nevirapine(05), atazanavir(02), nimesulide(01)	08	8.89
Stevens-Johnson Syndrome	nevirapine(04)	04	4.44
Fixed Drug Eruption	diclofenac(01), phenytoin(02)	03	3.33
Pustular rash	nevirapine(02)	02	2.22
Angiodema	nevirapine(02)	02	2.22
Exfoliative Dermatitis	phenytoin(01), dapsone(01)	02	2.22

[Table/Fig-4]: Morphological types of CADRs and the suspected drugs with frequency (n=90)

Causality	Number (%)
Definite	00 (00%)
Probable	52 (57.78%)
Possible	38 (42.22%)

[Table/Fig-5]: Causality Assessment of CADRs by WHO-UMC Causality assessment system (n=90)

Severity	Level	Number
Mild	Level 1	27
	Level2	44
	Total	71 (78.89%)
Moderate	Level 3	11
	Level 4a	02
	Level 4b	02
	Total	15 (16.67%)
Severe	Level 5	04
	Level 6	00
	Level 7	00
	Total	04 (4.44%)

[Table/Fig-6]: Severity Assessment of CADRs by Modified Hartwig and Siegel Scale (n=90)

The age range in our study was 3-67 years with majority of patients falling in the age group of 21-40 years. This is similar to other studies and shows that no age is exempted from CADRs [17,18].

In present study, females were predominantly affected by CADRs and male to female ratio was 1:2.33. Earlier studies have shown either female preponderance [6], male preponderance [17] or no gender difference [18]. Predominance of females in present study could be explained by the fact that most of CADRs in the study were attributed to anti-retroviral medications (nevirapine in particular) and previous studies indicate potential gender differences in the frequency and severity of CADRs to anti-retroviral drugs [19]. It is well known that pharmacokinetics and/or pharmacodynamics of a drug may differ in males and females but how these differences lead to increased frequency of ADRs for certain drugs in females is not precisely known [20].

The causative agents and pattern of CADRs differs from centre to centre depending upon the drugs used and services offered. Our hospital has Anti-Retroviral Therapy (ART) centre established in the year 2004 and regularly provides ART to HIV positive patients. HIV infected patient's present complex immunological alterations which pose these patients at a higher risk of developing CADRs due to drug hypersensitivity [21].

The present study found that antiretroviral drug nevirapine (NVP) was most commonly associated with CADRs in an outpatient setting. NVP was incriminated in 39 cases of MP rash out of 69 (39/69, 56.12%) and 5 cases of urticaria out of 8 cases (5/8, 62.5%). All four cases of SJS, two cases of pustular rash and two cases of angioedema were attributed to NVP [Table/Fig-4].

NVP is most commonly used non-nucleoside reverse transcriptase inhibitor (NNRTI) as a part of first-line ART. According to the revised National AIDS Control Organization (NACO) ART initiation guidelines November 2011, ART should be started if CD4 count is < 350 cells/mm^3 in stages 1& 2 and irrespective of CD4 count in stages 3 & 4. It is also mentioned by NACO that patients who initially were on NVP-based ART and shifted to efavirenz due to anti-tubercular treatment (ATT) should again be shifted to NVP without any lead in dose after completion of rifampicin-based ATT [22].

A recent study by Lokhande et al., has shown that there is striking increase in the incidence of NVP-induced cutaneous rashes of all forms (4.64% patients treated before November 2011 vs 9.03% patients treated after November 2011) and considerable increase in frequency of severe kind of reactions with the revised guidelines [23]. Number of previous studies has shown NVP to be the most common anti-retroviral agent associated with CADRs including severe CADRs like Stevens-Johnson syndrome, Toxic epidermal necrolysis and Stevens-Johnson Syndrome-Toxic epidermal necrolysis overlap [24-27].

Evidence suggests that there is strong genetic predisposition to cutaneous reactions with NVP and certain Human Leukocyte Antigen (HLA) genotypes are strongly associated with CADRs [28,29]. Generation of electrophilic quinoid species during NVP metabolism and their covalent reaction with bionucleophiles has also been suggested to be possible underlying mechanism for NVP toxicity [30].

Besides NVP, other anti-retroviral drugs namely efavirenz, zidovudine, lamivudine and atazanavir were also suspected in CADRs especially MP rash in present study [Table/Fig-4]. Earlier studies showing anti-retroviral medications associated with diverse and frequent skin manifestations support our finding [31,32].

In present study, anti-retroviral medications were suspected to be responsible in more than 75% of cases. In remaining 25% of cases, anti-bacterials, anti-epileptics and NSAIDs were suspected to be culprits. Antimicrobials, NSAIDs, and anti-epileptics have been consistently reported to be causative agents in CADRs by several studies. In a systematic review by Patel et al., based on 18 prospective studies of CADRs during January 1995 to April 2013, major drugs associated with CADRs were antimicrobials (45.46%), NSAIDs (20.87%) and anti-epileptics (14.5%) [5]. A prospective, observational study in an outpatient setting by Saha et al., found that antimicrobials (sulfonamides, fluoroquinolones, and β lactams), analgesics and anti-epileptics accounted for most of CADRs [18]. Despite established ART centre, this study did not report any CADR to anti-retroviral medications probably due to practice of managing ART-induced ADRs by the ART centre itself. Other studies conducted in an out-patient setting also indicate that antimicrobials, anticonvulsants and NSAIDs are commonly associated with CADRs in an out-patient setting [33,34]. Here again, anti-retroviral drugs were not reported to cause CADRs indicating variation in drug-use or practices-followed.

The most common morphological pattern of CADR in our study was MP rash followed by urticaria, SJS and fixed dose eruption. Our findings are supported by several previous studies [18,27,33,34] and a systematic review by Patel et al., [5].

The causality assessment was probable in 57.78% and possible in 42.42% of cases in our study which is similar to previous studies [34]. Majority of CADRs (96%) belonged to category of mild to moderate severity while about 4% of reactions were severe. Earlier studies support this finding [5,34].

There are some limitations to present study. As most of the patients attending OPD of this hospital come from lower socio-economic strata and primarily rely on drugs supplied free of cost by the hospital, the suspect-drug data and pattern of CADRs generated

from this study may not be reflective of the pattern of other tertiary care centers catering to patients of higher socio-economic strata or offering different services than ours. Causality assessment is not always straight-forward especially in polypharmacy cases and none of the case in our study could be classified as definite as rechallenge was not attempted deliberately in out-patient setting owing to potential risk associated with it. In this regard, it is interesting to know that in a study by Gangar et al., [35], an attempt to rechallenge with NVP or delaviridine resulted in recurrence of rash in >75% patients and in 70% who were crossed over to the alternative agent.

Some patients with minor, self-limiting drug eruptions may not have reported to skin OPD in present study and might have been treated by other departments. This is suggested by our observation that >66% of patients of MP rash belonged to Grade 3.

CONCLUSION

Anti-retroviral drugs especially NVP was suspected in most of the CADRs in an outpatient setting of a tertiary care hospital providing ART. Older drugs i.e. antimicrobials, NSAIDs and anti-epileptics still caused substantial CADRs. MP rash was most common morphological pattern while severe life-threatening CADRs occured in 4% of cases. Female gender was twice as susceptible to CADRs as male gender.

With increasing recognition of variety of clinical manifestations of CADRs with anti-retroviral and other drugs, elucidation of underlying cellular and molecular mechanisms is needed. Deeper understanding of underlying mechanisms coupled with identification of risk factors for serious CADRs and appropriate genetic screening of groups at higher risk may improve outcomes of skin reactions in future.

REFERENCES

[1] 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.

[2] Jose J, Rao PG. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. *Pharmacol Res*. 2006;54(3):226-33.

[3] Shrivastava M, Uchit G, Chakravarti A, Joshi G, Mahatme M, Chaudhari H. Adverse drug reactions reported in Indira Gandhi government medical college and hospital, Nagpur. *JAPI*. 2011;59:1-4.

[4] Svensson CK, Cowen EW, Gaspari AA. Cutaneous drug reactions. *Pharmacol Rev*. 2001;53(3):357–79.

[5] Patel TK, Thakkar SH, Sharma DC. Cutaneous adverse drug reactions in Indian population: A systematic review. *Indian Dermatol Online J* [serial online]. 2014 [cited 2015 Jun 29];5 Suppl S2:76-86. Available from: http://www.idoj.in/text.asp?2014/5/6/76/146165

[6] Chatterjee S, Ghosh AP, Barbhuiya J, Dey SK. Adverse cutaneous drug reactions: A one year survey at a dermatology outpatient clinic of a tertiary care hospital. *Indian J Pharmacol* [serial online]. 2006 [cited 2015 Jun 30];38:429-31. Available from: http://www.ijp-online.com/text.asp?2006/38/6/429/28212

[7] Shear NH, Knowles SR. Cutaneous reactions to drugs. In: Goldsmith WL, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, editors. Fitzpatrick's Dermatology in General Medicine, 8th edn. USA: McGraw-Hil; 2012. pp. 449-57.

[8] Chaponda M, Pirmohamed M. Hypersensitivity reactions to HIV therapy. *Br J Clin Pharmacol*. 2010;71(5):659–71.

[9] Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: Part I: Inhibitors of the cellular membrane. *J Am Acad Dermatol*. 2015;72(2):203-18.

[10] Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: Part II: Inhibitors of intracellular molecular signaling pathways. *J Am Acad Dermatol*. 2015;72(2):221-36.

[11] Rezakovic S, Pastar Z, Kostovic K. Cutaneous adverse drug reactions caused by antituberculosis drugs. *Inflamm Allergy Drug Targets*. 2014;13(4):241-48.

[12] The role of national centres. World Health Organization - international drug monitoring 1972. Technical report series 498, Geneva.

[13] Shinkai K, Stern RS, Wintroub BU. Cutaneous Drug Reactions. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J (eds.) Harrison's Principles of Internal Medicine. 18th edition. USA: McGraw-Hil; 2012. Pp. 432-40.

[14] US Department of Health and Human Services, NIH, NCI. Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0, published: 28 May 2009 (ver. 4.03: 14 June 2010). [16 Jul 2015, date last accessed]. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

[15] World Health Organization-Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment [Internet]. [cited 2015 February 23]. Available from: http://who-umc.org/Graphics/24734.pdf

[16] Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm*. 1992;49:2229-32.

[17] Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: Clinical pattern and causative agents - A 6 year series from Chandigarh, India. *J Postgrad Med*. 2001;47:95-99.

[18] Saha A, Das NK, Hazra A, Gharami RC, Chowdhury SN, Datta PK. Cutaneous adverse drug reaction profile in a tertiary care outpatient setting in eastern India. *Indian J Pharmacol*. 2012;44:792-97.

[19] Ofotokun I, Pomeroy C. Sex differences in adverse reactions to antiretroviral drugs. *Top HIV Med*. 2003;11:55-59.

[20] Rademaker M. Do women have more adverse drug reactions? *Am J Clin Dermatol*. 2001;2(6):349-51.

[21] Yunihastuti E, Widhani A, Karjadi TH. Drug hypersensitivity in human immunodeficiency virus-infected patient: challenging diagnosis and management. *Asia Pac Allergy*. 2014;4(1):54-67.

[22] National AIDS Control Organization. Antiretroviral Therapy Guidelines for HIV Infected Adults and Adolescents Including Post Exposure Prophylaxis. New Delhi: Ministry of Health and Family Welfare, Government of India; 2013 May.

[23] Lokhande AJ, Sutaria A, Shah BJ, Shah AN. Changing incidence of nevirapine-induced cutaneous drug reactions: After revised guideline Nov 2011. *Indian J Sex Transm Dis*. 2013;34(2):113-18.

[24] Barvaliya M, Sanmukhani J, Patel T, Paliwal N, Shah H, Tripathi C. Drug-induced Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS-TEN overlap: a multicentric retrospective study. *J Postgrad Med*. 2011;57(2):115-19.

[25] Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The Euro SCAR-zstudy. *J Invest Dermatol* [*Internet*]. 2007 [cited 2015 Jul 16];128(1):35-44. Available from: http://www.nature.com/jid/journal/v128/n1/full/5701033a.html

[26] Kondo W, Carraro EA, Prandel E, Dias JM, Perini J, Macedo RL, et al. Nevirapine-induced side effects in pregnant women: experience of a Brazilian university hospital. *Braz J Infect Dis*. 2007;11(6):544-48.

[27] Sharma A, Vora R, Modi M, Sharma A, Marfatia Y. Adverse effects of antiretroviral treatment. *Indian J Dermatol Venereol Leprol.* 2008;74(3):234-37.

[28] 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(4):540-41.

[29] Sukasem C, Puangpetch A, Medhasi S, Tassaneeyakul W. Pharmacogenomics of drug-induced hypersensitivity reactions: challenges, opportunities and clinical implementation. *Asian Pac J Allergy Immunol*. 2014;32(2):111-23.

[30] Antunes AM, Novais DA, da Silva JL, Santos PP, Oliveira MC, Beland FA, et al. Synthesis and oxidation of 2-hydroxynevirapine, a metabolite of the HIV reverse transcriptase inhibitor nevirapine. *Org Biomol Chem*. 2011;9:7822-35.

[31] Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part I. Lipodystrophy syndrome, nucleoside reverse transcriptase inhibitors, and protease inhibitors. *J Am Acad Dermatol*. 2010;63(4):549-61.

[32] Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part II. Nonnucleoside reverse transcriptase inhibitors, entry and fusion inhibitors, integrase inhibitors, and immune reconstitution syndrome. *J Am Acad Dermatol*. 2010;63(4):563-69.

[33] Gohel D, Bhatt SK, Malhotra S. Evaluation of Dermatological Adverse Drug Reaction in The Outpatient Department of Dermatology at a Tertiary Care Hospital. *Indian Journal of Pharmacy Practice*. 2014;7(3):42-49.

[34] Anjaneyan G, Gupta R, Vora R. Clinical Study of Adverse Cutaneous Drug Reactions at a Rural Based Tertiary Care Centre in Gujarat. *Natl J Physiol Pharm Pharmacol*. 2013;3(2):129-36.

[35] Gangar M, Arias G, O'Brien JG, Kemper CA. Frequency of cutaneous reactions on rechallenge with nevirapine and delavirdine. *Ann Pharmacother*. 2000;34(7-8):839- 42.

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