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Anti-Retroviral Treatment in dr. Sardjito Central General Hospital Yogyakarta

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ABSTRACT

Background: Adverse cutaneous drug reactions (ACDRs) affect 2-3% of hospitalized patients globally, wherein approximately 2% (1 in 1,000 cases) accounted for a severe form of cutaneous drug reactions. Out of all dermatologic diagnoses recorded by HIV patients, eight-point twenty-five percent of patients feature ACDRs, indicating that these patients are 100 times more inclined to develop unfortunate, severe reactions to anti-retroviral treatment. Therefore, there is an urgency in identifying the prevalence of ACDRs in HIV patients taking anti-retroviral treatment. **Purpose:** The aim of this study is to calculate the prevalence of anti-retroviral drug-induced ACDRs in HIV-positive patients in dr. Sardjito Central General Hospital, in the time period of January 2015 to December 2017. **Methods:** This study analyzed inpatient and outpatient medical records from January 2015 to December 2017 in the Dermatology and Venereology Department of dr. Sardjito Central General Hospital, which recorded ART-induced ACDRs manifestations. **Result:** This study revealed a prevalence of 0.095% of ACDRs as a result of ART administration, with 1.5% HIV-positive patients affected by ACDRs in response to ART medication. A male:female sex ratio of 2:1 with an average age of 30.4 ± 5.94 years old was found. The most predominant type of ACDR found in HIV-positive patients receiving ART was maculopapular rash (46.7%), while the most common type of drug within the ART regimen to cause such ACDR was Nevirapine (25.8%). **Discussion:** Nevirapine was the most common type of causative drug, for monotherapy (22.6%) and polytherapy (25.8%).

Keywords*:* Adverse cutaneous drug reactions, ART regimen, nevirapine, maculopapular rash, HIV-positive patients.

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BACKGROUND

Adverse cutaneous drug reactions (ACDRs) refer to undesirable responses skin manifestation as a consequence of drug administration. These reactions may unfortunately impact the skin's structure or function, appendages, or mucous membranes. Globally, ACDRs affect two to three percent of hospitalized patients around the globe experience ACDRs, with roughly 2% (1 in 1,000 occurrences) resulting in a severe form of cutaneous drug reactions.[1] Patients with HIV were prone to experience these severe adverse reactions from antiretroviral treatment.[2]

ACDRs accounted for 6% of all dermatologic diagnoses manifesting in HIV-positive patients after assessing a total of 150 HIV patients in Infectious Diseases and Medical Centre, Voluntary Health Services, India.[3] The most predominant form of ACDRs is morbiliform rash, followed by urticaria.

It is quite a challenge to diagnose and treat drug hypersensitivity in HIV-positive patients, as these patients are vulnerable to opportunistic infections, and

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receive at least 3 distinct drugs. All of the drugs have differing sites of action, referred to as anti-retroviral therapy (ART) regimen.

A study in 2019 by Peter et al.[4] mentioned a hundredfold risk of HIV-positive patients in developing ACDRs in comparison to immune-competent patients. This then highlights the urgency of early detection and identification of drugs that may potentially lead to an eruption, which is pivotal in preventing mortality by severe cutaneous drug reactions.

It is worthwhile to note the urgency in addressing and noting the prevalence of these ACDRs, especially in HIV-positive patients undergoing an ART regimen. This study aims to investigate the prevalence of ACDRs diagnoses in HIV-positive patients recorded in dr. Sardjito Central General Hospital. This study analyzed the medical records of the Dermatology and Venereology inpatient and outpatient clinics registered in the time period of January 2015 to December 2017. We gathered eligible data from this pool of medical records using inclusion and exclusion criteria explained further later in this study.

METHODS

This retrospective, record-based study analyzed retrospective data of HIV-positive inpatient and outpatient medical records in the Dermatology and Venereology department undergoing an ART regimen. The complaints of ACDRs were maculopapular rash, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), and acute generalized exanthematous pustulosis (AGEP).

We gathered and filtered eligible data from documented medical records in dr. Sardjito Central General Hospital Yogyakarta, within the 3-year time period of January 2015 to December 2017. Subjects excluded from this study refer to (1) medical records containing other types of ACDRs aside from maculopapular morbilliform, SJS/TEN, DRESS, AGEP; (2) medical records that merely included the history of the four mentioned ACDRs, with the ACDRs progression occurring outside the time period determined by this study (January 2015 – December 2017); and (3) medical records coding for one of the four observed ACDRs that were, either definitively or presumably, non-drug induced. The filtered eligible data will be measured using CRF adapted from RegiSCAR and analyzed with the use of Microsoft Excel. Patch test was not routinely done to diagnose ACDRs. ACDRs were mostly determined through clinical findings, however the eligible medical records noted that the patients did not receive other medications aside from the ART regimen, therefore the causative drug could be in deduced.

The data analysis for this study makes use of frequency tests (descriptive) from the demographic data of the patients, including age, sex, onset of ACDRs secondary to ART administration, presence of comorbidities, the predominant type of ART, and the predominant ACDR variant in response to ART regimen. This research has been reviewed by the Ethics Committee at the Faculty of Medicine, Gadjah Mada University, dr. Sardjito General Hospital (KE/FK/1111/EC October 19th 2018).

RESULT

From the sample of 15 patient records, 10 consisted of male patients (66.7%; male-female M:F sex ratio 2:1). There was a recorded average age of 30.4 ± 5.94 years old, while the affected age population ranged from 18 to 38 years old. In the years between 2015 and 2017, dr. Sardjito Central General Hospital treated 1,028 HIV patients in total. Of those, 15 developed ACDRs after starting an ART regimen, which translates to a 1.5% prevalence within the treated HIV population.

A total of 173 patients had at least one of the aforementioned ACDRs. There was an aggregate of 15,711 cases recorded in the Dermatology and Venereology department in dr. Sardjito Central General, accumulated over 3 years within the span of January 2015 to December 2017. Out of the 15,711 cases, 173 medical records had presented with the type of ACDRs evaluated in this study, 15 of which were recorded to receive an ART regimen and fulfilled the inclusion and exclusion criteria of this study. Therefore, the prevalence of patients who had ACDRs as a result of receiving ART was 0.095%.

From Table 1, focuses exclusively on the 15 cases of ACDRs brought on by medications included in the ART regimen. It reveals that EM (46.7%) remains the most common kind of ACDRs, closely followed by SJS (40%), DRESS (6.7%), and TEN (6.7%). The existing trend between the two sets of data is similar in that the prominent ACDR type was shown to be EM, and subsequently SJS, DRESS, then TEN. It is worthy to note that in the different ACDRs observed in patients who underwent ART dataset, there was an absence of AGEP and SJS/TEN cases. The 15 medical records examined corroborated that 46.7% of the patients were subjected to a fixed drug combination (FDC) of ART

regimen, which consisted of "Tenofovir + Lamivudine + Efavirenz", whereas the remaining 53.3% patients received an ART regimen of "Tenofovir + Lamivudine + Nevirapine".

Overall, Nevirapine was the drug mostly suspected as the causative agent of all types of ACDRs (25.8%), and subsequently Tenofovir, Efavirenz and Lamivudine, each of which contributed to 22.6% of the occurrence of ACDRs, showing merely a 0.8% difference. Lamivudine was the presiding drug inducing the onset of EM (19.4%), followed by Tenofovir (16.1%), Efavirenz (12.9%) and Nevirapine (6.5%). The one case of DRESS observed in this study was caused by a combination of "Tenofovir + Emtricitabine + Efavirenz", thus each individual drug has a 3.2% chance of inducing the mentioned ACDRs. In contrast with EM, Nevirapine was the key factor in the occurrence of SJS (12.9%) and was the sole offending drug causing TEN. In general, ART was accountable to potentially be the offending drugs of the 15 reported cases of EM, DRESS, SJS, and TEN (Table 2).

Table 1. Adverse Cutaneous Drug Reactions in patients receiving ART

ACDRs observed	Frequency	Percentage (%)
EM	7	46.6
DRESS	1	6.7
AGEP	0	0
SJS	6	40
SJS/TEN	0	0
TEN	1	6.7
Total	15	100

ACDRs= adverse cutaneous cutaneous drug reactions; EM = erythema multiforme; DRESS = Drug reaction with eosinophilia and systemic sysmptoms; AGEP = Acute generalized exanthematous pustulosis; SJS = Stevens-Johnson syndrome; TEN = toxic

Table 2. Suspected drugs (in total) depending on the nature of ACDRs

Type of ACDRs	Suspected Drugs									
	LPV/r	NVP	EFV	AZT + 3TC	3TC	d4T	AZT	TDF	FTC	RAL
EM	0	2	4	0	6	0	0	5	0	0
DRESS	0	0	1	0	0	0	0	1	1	0
AGEP	0	0	0	0	0	0	0	0	0	0
SJS	0	5	2	1	1	0	0	1	0	0
SJS/TEN	0	0	0	0	0	0	0	0	0	0
TEN	0	1	0	0	0	0	0	0	0	0
Total	0	8	7	1	7	0	0	7	1	0

Note: LPV/r = Lopinavir/Ritonavir; NVP = Nevirapine; EFV = Efavirenz; 3TC = Lamivudine; d4T = Stavudine; AZT = Zidovudine; TDF = Tenofovir; FTC = Emtricitabine; RAL = Raltegravir.
ACDRs = adverse cutaneous drug reactions; EM = erythema multiforme; DRESS = Drug reaction with eosinophilia and systemic symptoms; AGEP = Acute generalized exanthematous pustulosis; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

Out of 15 reported cases of ART-induced ACDRs, 7 of them revealed records of patients who were on polytherapy (46.7%) with other drugs in addition to those of the ART regimen. The remaining 53.3% represented ACDRs solely caused by ART. The results showed a predominance of Nevirapine as the suspected drug even in the monotherapy regimen (22.6%), identical to the results of Table 2, which shows the prevalence of ACDRs among all reported cases regardless of monotherapy or polytherapy. However, as Table 2 demonstrates, Tenofovir, Efavirenz and Lamivudine only have a 0.8% difference in prevalence

with Nevirapine; Table 3 exhibits a much lesser value for all 3 drugs, specifically 12.9%, 3.2%, and 9.7% respectively. With the absence of drugs other than ART, rather than having the same value for the 3 drugs priorly mentioned, Tenofovir had the greatest prevalence (12.9%) among Efavirenz and Lamivudine (Table 3).

Among the 7 reported cases of polytherapy, there was a total of 23 drugs other than ART administered to the patients noted by EM, DRESS and SJS manifestations. NSAIDs were the most often recommended drug type for HIV-positive patients receiving ART (30.43%), which partially explains their widespread use. In the EM group, both NSAIDs and antibiotics prevail as the dominant drug types included in the polytherapy regimen alongside ART, with an individual prevalence of 21.74%. The one case of DRESS found in the period of this study substantiated the use of an antibiotic in addition to the ART prescribed to the patient. In patients documented with SJS manifestation, there was an identical frequency of both NSAIDs and antibiotic use, each accounting a prevalence of 8.70%.

We found comorbidities in 8 out of 15 analyzed medical records, thus giving a prevalence of 53.3%. The most frequent comorbidity was drug-induced hepatitis with a value of 30.77%, followed by tuberculosis (TB) with a prevalence of 23.08%. Following the trend, drug-induced hepatitis was the prevailing type of comorbidity in reported cases of EM (23.08%), with community-acquired pneumonia following suit (15.38%).

Table 3. Incidence of different types of ACDRs according to ART monotherapy

Type of ACDRs	Suspected Drugs									
	LPV/r	NVP	EFV	AZT + 3TC	3TC	d4T	AZT	TDF	FTC	RAL
EM	0	2	1	0	3	0	0	3	0	0
DRESS	0	0	0	0	0	0	0	0	0	0
AGEP	0	0	0	0	0	0	0	0	0	0
SJS	0	4	0	1	0	0	0	1	0	0
SJS/TEN	0	0	0	0	0	0	0	0	0	0
TEN	0	1	0	0	0	0	0	0	0	0
Total	0	7	1	1	3	0	0	4	0	0

Note: LPV/r = Lopinavir/Ritonavir; NVP = Nevirapine; EFV = Efavirenz; 3TC = Lamivudine; d4T = Stavudine; AZT = Zidovudine; TDF = Tenofovir; FTC = Emtricitabine; RAL = Raltegravir.
ACDRs = adverse cutaneous drug reactions; EM = erythema multiforme; DRESS = Drug reaction with eosinophilia and systemic symptoms; AGEP = Acute generalized exanthematous pustulosis; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

DISCUSSION

The most affected age population in average was those who were 30.4 ± 5.94 years old, ranging from the ages 18 to 38 years old. Comparably, Patel et al.[5] exhibited a preponderance of 31-40-year-olds (24.44%). This study found that ACDRs happened more often in men than in women (M:F sex ratio 2:1), which is similar to a study by Patel et al.[5] (males were more likely than females, 1.2:1). This was also noted in another study by Maharani et al.[6], in which a high number of cutaneous drug reactions cases were found in adult males between 20-39 years old with low CD4 count.[6]

We observed a trend of declining predominance from EM (46.7%) to SJS (40%), DRESS (6.7%), and TEN (6.7%) among all 15 reported cases of ART-induced ACDRs in dr. Sardjito Central General Hospital. In line with the findings of this study, Patel et al.[5] found that maculopapular rash (28.56%) was the common variant of ACDRs manifested seen in HIV-positive patients receiving ART therapy. It was followed by SJS, SJS/TEN, TEN and erythema multiforme, each accounting for 14.28%; and finally, DRESS (9.52%).

Kouotou, E.A. et al.[7] who demonstrated that a benign form of drug eruptions, such as maculopapular exanthema also known as maculopapular rash or EM,

is the most common type of ACDRs, corroborate the preponderance of EM in this study. We found that maculopapular rash, also known as EM, was the most common type of ACDR among HIV-infected patients, followed by SJS, DRESS, and FDE. Similarly, maculopapular rash and SJS were the most common ACDR types seen in the general population.[8,9]

Based on the results, Nevirapine had a predominance over other types of drugs in the ART regimen whether it was monotherapy or polytherapy, with a prevalence of 22.6% and 25.8% respectively. SJS was found to be induced primarily by Nevirapine (12.9%). Belonging to the NNRTI family, despite the unclear exact mechanism causing ACDRs, speculation suggests that there is a genetic predisposition to cutaneous reactions with Nevirapine, along with its metabolism in the human body, play a role in its toxicity.[1,10]

Nevirapine was also noted to be the major causative drug in inducing allergies, wherein mild drug eruptions may develop into severe forms of drug eruptions, mainly ACDRs.[11,12] Another study also noted that in addition to Nevirapine, Efavirenz was also one of the main ACDR-inducing drug.[13] Predisposing factors for drug hypersensitivity, mainly ACDRs, typically include a specific immunologic structure, a larger molecular mass, reactive metabolites, the route of drug administration (parenteral/topical), specific immunologic structure, frequent therapy courses, and a longer duration of exposure to the drug.[14,15]

The present study has limitations, such as the less specific ICD10 coding of the ACDRs. We code EM, DRESS and AGEP are coded under L27.0, which stands for "generalized skin eruption due to drugs and medicaments taken internally," thereby encompassing a vast spectrum of cutaneous reactions/diseases. This study did not include FDE, a type of ACDR, which may have contributed to the relatively low reported prevalence of ACDRs. Furthermore, there is no consensus on the severity grading of maculopapular rash, thus common clinical manifestations of said ACDRs are used instead. ACDRs induced by the ART regimen account for 0.095% of all dermatologic diagnoses in HIV-positive patient records between January 2015 to December 2017 in dr. Sardjito Central General Hospital. Among them, the leading ACDR variant recorded was EM (46.7%) followed closely by SJS (40%), DRESS (6.7%), and TEN (6.7%), all in descending order of prevalence. Finally, Nevirapine (25.8%) was more common than other types of drugs in the ART for monotherapy 22.6% (7/31) and for polytherapy 25.8% (8/31).

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