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The association of CD4 lymphocyte count with drug hypersensitivity reaction to highly active antiretroviral therapy, trimethoprim sulfamethoxazole, and antitubercular agents in human immunodeficiency virus patients

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ABSTRACT

Background: The introduction of highly active antiretroviral therapy (HAART) and antibiotic regimens for the treatment of human immunodeficiency virus (HIV) and its concomitant opportunistic infections, respectively, significantly improve the morbidity and mortality of the infected patients. However, these drugs commonly cause drug hypersensitivity reactions (DHRs) in patients with acquired immunodeficiency syndrome. The reason proposed are multifactorial, which includes immune hyperactivation, changes in drug metabolism, patient cytokine profiles, oxidative stress, genetic predisposition, and the principal target in HIV patients, the CD4+ lymphocytes.
Objective: This study determined the association of CD4 count and DHRs to first-line HAART, trimethoprim sulfamethoxazole, and antitubercular agents among HIV patients.
Methods: This is a retrospective analytical study. Review of charts were done. The demographic and clinical profile used a descriptive statistics such as mean and standard deviation for quantitative data and frequency and percent for categorical data. Chi-square and Fisher exact tests were used to measure the degree of the relationship of CD4 count and DHRs.
Results: A total of 337 eligible patients were included. There was a 25% incidence of hypersensitivity reactions. However, the prevalence of DHRs across the different CD4 groups was not statistically significant ($p = 0.167$). Likewise, the study found no significant association between the CD4 count and DHRs to first-line HAART, trimethoprim sulfamethoxazole, and antitubercular agents ($p = 0.311$). The most common DHR was morbilliform rash, and nevirapine was the most reported antiretroviral drug causing DHR.
Conclusion: There was no association in the CD4 count and DHRs to first-line HAART, trimethoprim sulfamethoxazole, and antitubercular agents. Hence, regardless of the baseline CD4 lymphocyte count, the physician should be vigilant in monitoring hypersensitivity reactions. Patient education on common DHRs is very important upon diagnosis of HIV and/ or initiation of treatment.

Keywords: Hypersensitivity; CD4 lymphocyte count; Highly active antiretroviral therapy; Trimethoprim sulfamethoxazole; Antitubercular agents; Human immunodeficiency virus

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INTRODUCTION

In the year 2020, there were 37.7 million people living with human immunodeficiency virus (PLHIV), with 1.5 million new HIV infections, and 680,000 deaths from acquired immunodeficiency syndrome (AIDS)-related causes. Of these, there were 10.2 million people who were not on HIV treatment [1]. In the Philippines, there were a total of 83,755 confirmed HIV-positive individuals, however, only 48,314 PLHIV were presently on antiretroviral therapy (ART) as of January 2021 [2].

The utilization of highly active antiretroviral therapy (HAART) has had a significant impact on the course and treatment of the disease and disease-related morbidity of HIV-infected patients. Its main goal is to provide and maintain viral load suppression to stop the disease progression, and generally, increase their life span and quality of life. The success of HAART in slowing the progression of HIV disease and in increasing the life expectancy of HIV patients is unfortunately accompanied with some significant downsides [3-9]. These disadvantages are principally related to a higher incidence of adverse drug reactions (ADRs), including drug hypersensitivity reactions (DHRs), which are more frequent in HIV patients than the general population [8, 10]. There has been a reported global incidence of 11% to 35.9% of ADRs to antiretroviral (ARV) drugs, and as high as 54% in the presence of opportunistic infections (OIs) such as tuberculosis, pneumocystis pneumonia (PCP) and toxoplasmosis [6-8]. A study by Davis and Shearer stated that the frequency of drug hypesensitivity among patients with HIV infection ranges from 3%–20% [9, 11]. The reason proposed are multifactorial, which includes immune hyperactivation, changes in drug metabolism, patient cytokine profiles, oxidative stress and genetic predisposition [9]. Additionally, there is a reduction in the number of CD4+ lymphocytes (T helper/Th)—the principal target in HIV patients, interference in the homeostasis, and function of other cells in the immune system. This event will further lead to disruption of the cellular and humoral immunity functions causing a wide clinical spectrum of diseases such as OIs, autoimmune reactions, and hypersensitivity reactions [8, 10].

These hypersensitivity reactions in HIV infected patients varies in severity and clinical manifestations [6-8]. They vary from cutaneous reactions, liver injury, anaphylaxis, to drug-induced anemia, neutropenia, thrombocytopenia, and other systemic manifestations [7]. The determination of DHRs in HIV patients is indeed challenging since these patients are on multiple drug regimens that are used to prevent and/or treat OIs.

Previously published studies have suggested that a lower CD4 count is associated with an increased prevalence of toxicities amongst those on HAART, antituberculosis drugs, and trimethoprim sulfamethoxazole [12-17]. Other studies have not found any association [9, 11, 18]. If such an association exists, then this could affect the patient's and clinician's decision to exert more vigilance in detecting hypersensitivity reactions during treatment.

So far, there is paucity of data in the Philippines on the DHRs to ARV drugs, and to commonly used concurrent medications such as trimethoprim sulfamethoxazole, and antitubercular agents. The objective of this study was to determine the association of the CD4 lymphocyte count with the prevalence and severity of DHRs to first-line ARV drugs tenofovir (TDF), lamivudine (3TC), efavirenz (EFV), zidovudine (AZT), nevirapine (NVP), trimethoprim sulfamethoxazole, and antitubercular agents (isoniazid [INH], rifampicin [RIF], ethambutol [ETH], and pyrazinamide [PZA]) among HIV patients. Demographic, clinical, and biochemical

profiles were also compared among patients with different baseline CD4 count. Findings of the study will greatly contribute to raising awareness, identification, and characterization of patients at risk, and in the early recognition and education on the signs and symptoms of various hypersensitivity reactions, and hence, guide patients to seek immediate treatment. Pertinent information or results may be used for treatment guidelines review, pharmaceutical planning, and clinician's decision-making prior to the initiation of medications.

MATERIALS AND METHODS

Design
This was a single-center, retrospective observational study conducted from January 2012 to June 2018.

Setting and participants
The study was conducted at the HIV/AIDS Core Team (HACT) Clinic of Southern Philippines Medical Center (SPMC), Davao City, the Philippines. SPMC is a government, primary treatment hub and/or referral center for HIV in the region with large number of HIV patients. All adult patients aged more than 18 years old with HIV confirmed and HIV-tuberculosis (TB) coinfection were included in the study. This criterion was based on the fact that patients of that age could give plausible report to health providers rather than children whose reports of hypersensitivity reaction(s) depended on their caregivers.

The following are the inclusion and exclusion criteria of the study:

Inclusion criteria
- Confirmation of HIV infection by enzyme-linked immunosorbent assay and/or Western blot.
- HIV positive patients who had received first-line, alternative first-line fixed dose combination of ARV therapy, as recommended by the Department of Health (DOH), for at least 1 month.
- HIV-TB coinfected patients on antituberculosis medications such as INH, RIF, ETH, and PZA.
- Patients should have a baseline CD4 count, complete blood count, fasting blood sugar, triglyceride level, total cholesterol, alanine aminotransferase, creatinine, estimated glomerular filtration rate (EGFR) based on chronic kidney disease-epidemiology collaboration equation, syphilis, hepatitis B surface antigen, antihepatitis C virus, gene expert, sputum acid fast-bacilli, and chest x-ray prior to the initiation of ART.

Exclusion criteria
- Patients switched to other ARV drugs due to ARV drug resistance
- All HIV patients started with second-line ARV agents as initial treatment

Study process
The study protocol was approved by the Department of Health XI Cluster Ethics Review Committee (DOH XI CERC) Davao City, the Philippines (CERC No. P18033001). Prior to enrollment, the investigator discussed the following to the patient: DHRs to HAART, antitubercular agents, and cotrimoxazole, role and importance of CD4 lymphocyte count, and the intent of the study. Written informed consent was obtained from the patients prior to their inclusion in the study.

The primary investigator utilized chart review of patient's records. A standardized data collection tool was used in recording clinical information from the patient. All identifying data of the patients remained anonymous. Hence, there was an assigned HACT nurse who prepared the charts to be reviewed. The identifying data of the patients in the chart were covered prior to data gathering. The anonymity of the data was done without the supervision of the primary researcher to ensure confidentiality.

DHRs were gathered based on patient's complaints, the symptoms, and signs, noted by the resident physician on the charts. DHRs due to ARV, cotrimoxazole and antitubercular agents were considered if it was absent prior to the initiation of the above said drugs.

Variables
The independent variables were the patient's CD4 lymphocyte count, ARV drugs, antitubercular agents, and cotrimoxazole, and demographic, clinical, and other biochemical parameters. Dependent variable was the patient's hypersensitivity reactions.

Sample size calculation
The sample size for this study was computed using a calculator in https://select-statistics.co.uk/calculators/sample-size-calculator-population-proportion/. The following assumptions were used in the calculation:
 (1) There were around 2,848 cases of confirmed HIV-AIDS enrolled in SPMC HACT clinic from 1999 to June 30, 2018, and among these, the total number of currently alive PLHIV on ART is 2491.
 (2) The rate of hypersensitivity reactions was 50%. In a study by Davis and Shearer, they reported that the incidence of DHR in HIV patients is 3%–20% [9], however, since there is paucity of data on the incidence of DHR in the Philippines, 50% was therefore used.
 (3) The significance level of the test was 0.05.
 (4) The total sample size needed for this study is 337.

Data handling and analysis
R software was used for the data analysis. Descriptive statistics was used such as mean, standard deviation, frequency, and percentages to summarize the demographic and clinical profile of the respondents. The parametric analysis of variance test and nonparametric Kruskal-Wallis test, and parametric t test and its nonparametric counterpart, the Mann-Whitney U test were used for the analysis of continuous and categorical data, respectively, to determine the differences between the 2 groups of patients. All tests used the 5% level of significance. A p value of <0.05 was considered statistically significant. Means and standard deviations were also used to determine the temporal relationship of the time to onset of DHR from the initiation of the drugs. To identify the association of CD4 count and hypersensitivity reactions in HIV patients, chi-square and Fisher exact tests were used to measure the degree of its relationship.

RESULTS

A total of 337 patients were included in the study. The patients were grouped according to their baseline CD4 count, such as: group 1 (CD4 <50 cells/mm³), group 2 (CD4 51–200 cells/mm³), group 3 (CD4 201–350 cells/mm³), group 4 (CD4 351–499 cells/mm³), and group 5 (CD4 ≥500 cells/mm³).

Table 1. Comparison of the demographic, clinical profile, and biochemical findings of HIV patients

Characteristic	CD4 count					p value
	<50	51–200	201–350	351–499	≥500	
CD4 count	24.42 ± 3.45	105.69 ± 3.56	277.45 ± 6.43	437.1 ± 7.89	638.46 ± 10.2	<0.001
Age (yr)	28.25 ± 1.09	29.4 ± 1.32	27.6 ± 0.97	27.76 ± 1.43	29.12 ± 1.51	0.435
Sex						0.191
Male	110 (94)	103 (88)	59 (50.4)	26 (96.3)	24 (88.9)	
Female	6 (5.1)	4 (3.4)	2 (1.7)	1 (3.7)	2 (7.4)	
Pregnant	1 (0.9)	1 (0.9)	0 (0)	0 (0)	1 (3.7)	
BMI (kg/m²)	21.5 ± 3.22	21.73 ± 1.29	21.82 ± 4.56	21.68 ± 2.45	23.07 ± 2.97	0.75
Status upon diagnosis						0.032
Asymptomatic	4 (3.4)	24 (20.7)	43 (37.1)	18 (66.7)	23 (88.5)	
Symptomatic	112 (96.6)	83 (71.6)	18 (15.5)	9 (33.3)	3 (11.5)	
No comorbidities	24 (12.1)	42 (29.6)	41 (65.1)	21 (75)	14 (50)	0.035
HIV without tuberculosis	62 (26)	74 (32)	54 (23)	23 (10)	21 (9)	0.0001
HIV with tuberculosis	54 (52)	32 (31)	7 (7)	5 (5)	5 (5)	
Syphilis	5 (2.5)	5 (3.5)	3 (4.8)	0 (0)	0 (0)	0.418
Hepatitis B	8 (4)	7 (4.9)	3 (4.8)	0 (0)	1 (3.6)	0.993
Hepatitis C	0 (0)	2 (1.4)	0 (0)	0 (0)	0 (0)	0.981
Oral candidiasis	46 (23.2)	18 (12.7)	1 (1.6)	1 (3.6)	0 (0)	0.532
PCP pneumonia	33 (16.7)	2 (1.4)	0 (0)	0 (0)	0 (0)	0.661
CMV retinitis	4 (2)	6 (4.2)	0 (0)	0 (0)	0 (0)	0.996
Dyslipidemia	5 (2.5)	4 (2.8)	3 (4.8)	1 (3.6)	2 (7.1)	0.998
Hypertension	0 (0)	0 (0)	1 (1.6)	0 (0)	2 (7.1)	0.986
Diabetes mellitus type 2	0 (0)	0 (0)	2 (3.2)	0 (0)	3 (10.7)	0.998
Complete blood count						
Hemoglobin	123.33 ± 10.92	134.04 ± 11.37	141.05 ± 11.36	148.31 ± 12.42	147 ± 12	0.021
White blood count	6.83 ± 1.11	7 ± 1.56	7.32 ± 1.55	9.76 ± 2.61	7.82 ± 2.12	0.043
Neutrophils	61.86 ± 4.3	56.68 ± 4.75	56.55 ± 4.74	160.83 ± 5.8	52 ± 4.7	<0.01
Lymphocytes	23.89 ± 3.2	28.52 ± 3.65	31.88 ± 3.64	32 ± 4.7	35.59 ± 6.7	0.010
Monocytes	7.76 ± 0.98	7.64 ± 1.43	6.7 ± 1.42	5.38 ± 2.48	6.42 ± 0.78	0.342
Eosinophils	5.94 ± 0.78	6.3 ± 1.23	4.43 ± 1.22	4.76 ± 2.28	5.15 ± 0.69	0.327
Basophils	0.45 ± 0.12	0.4 ± 0.57	0.37 ± 0.56	0.55 ± 1.62	0.65 ± 0.11	0.230
Platelet count	270.09 ± 21.7	282.43 ± 22.15	295.5 ± 22.14	264.79 ± 23.2	288.69 ± 23.6	0.187
EGFR	113.53 ± 1.21	112.07 ± 1.66	115.1 ± 1.65	112.32 ± 2.71	119.25 ± 2.3	0.218
ALT	45.3 ± 42.4	47.9 ± 56.3	41.5 ± 33.1	34.2 ± 28.7	59.3 ± 64.0	0.514
FBS	4.97 ± 0.77	4.89 ± 0.58	4.98 ± 0.95	5.06 ± 0.86	6.02 ± 3.3	0.500
Total cholesterol	3.77 ± 1.12	4.01 ± 1.22	3.95 ± 0.94	4.11 ± 0.96	4.31 ± 1.09	0.098
Triglyceride	1.48 ± 0.76	1.43 ± 0.72	1.45 ± 0.69	1.5 ± 0.63	1.5 ± 0.76	0.909

Values are presented as mean ± standard deviation or number (%).
HIV, human immunodeficiency virus; BMI, body mass index; PCP, pneumocystis pneumonia; CMV, cytomegalovirus; EGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; FBS, fasting blood sugar.

Demographic, clinical profile, and biochemical findings

Table 1 shows the comparison of demographic, clinical profile, and biochemical findings of patients included in the study.

The mean age of diagnosis was 28 years old (range, 18–56 years old), and 322 patients (95.55%) were comprised of males. There were only 11 female patients (3.26%) included, and among these, 3 patients were pregnant. The mean CD4 count was 180 cells/mm³ with a median CD4 of 99 cells/mm³.

Majority of the patients were symptomatic at the time of diagnosis (n = 225, 66.8%). Of these, 112 (96.6%) had CD4 of less than 50 cells/mm³, and 83 patients (71.6%) had CD4 of 51–200 cells/mm³. The incidence of tuberculosis coinfection was only 31% (n = 103), and it was frequently noted in patients with CD4 of less than 50 cells/mm³. Other commonly reported concurrent infections were syphilis, hepatitis B, oral candidiasis, and PCP pneumonia. However, its occurrence had no significant difference among the patients.

The difference in the patient's hemoglobin, white blood cell count, neutrophilic and lymphocytic counts were statistically significant. However, hematocrit, monocytes, eosinophils, basophils, platelet count, and EGFR had no significant difference across the different groups.

The most initiated ARV was a fixed-dose combination of TDF + 3TC + EFV (62.91%) followed by alternative first line ARVs such as AZT + 3TC + NVP (19%), AZT + 3TC + EFV (16.9%), and TDF + 3TC + NVP combination with (1.2%).

There were 107 subjects (32%) who had HIV-TB coinfection and these patients are on HRZE treatment. Additionally, there were 201 patients (60%) who were on INH prophylaxis.

Cotrimoxazole, the mainstay of treatment in PCP pneumonia, is currently recommended by the World Health Organization to be initiated in PLHIV with CD4 count of <200 cells/mm^3, and is only discontinued once the CD4 count improve to >200 cells/mm^3 for at least 2 CD4 count determination, and after 3 months of HAART [3]. In this study, there were 208 patients (62%) on cotrimoxazole for the treatment and/or prophylaxis of PCP pneumonia.

The mean CD4 counts of the patients before and after 6 months of ARV treatment were shown (**Table 2**).

It was noted that there was a statistically significant increase in the CD4 count of the patients after the different fixed-dose combination ARV drugs were initiated.

The incidence of DHRs to ARV, cotrimoxazole, and antituberculosis drugs was 25% (83). As shown in **Table 3**, DHRs were observed in mostly across the different CD4 groups, and it was dominantly seen in patients with CD4 count of less than 200 cells/mm^3. Specifically, DHRs occurred in 35% of patients in group 1, 37% in group 2, 17% in group 3, 10% in group 4, and only 1% in group 5. There was no significant difference in the occurrence of hypersensitivity reactions among the patients across the different CD4 groups. Furthermore, there was no significant difference on the drugs that caused the hypersensitivity reactions across the different CD4 groups.

Morbilliform form rash (47%) was noted to be the most common hypersensitivity reaction regardless of the CD4 count (**Table 4**). This was then followed by hemolytic anemia (13%), erythema multiforme (8%), and lastly, urticaria and thrombocytopenia with an incidence of 6% each. Other reported hypersensitivity reactions include angioedema, bronchospasm, anaphylaxis, granulocytopenia, dyslipidemia, hepatitis, gynecomastia, serum sickness, and

Table 2. Mean CD4 count of the Subjects before and after 6 months of antiretroviral therapy

Lab results	CD4 count		*p* value
	Baseline	After 6 months	
First-line ARV drugs			
TDF + 3TC + EFV	186.43 ± 21.14	274.05 ± 23.64	0.044
AZT + 3TC + EFV	224.23 ± 36.59	304.32 ± 40.91	0.024
Alternative first-line ARV drugs			
AZT + 3TC + NVP	171.29 ± 45.53	295.14 ± 50.91	0.018
TDF + 3TC + NVP	166.50 ± 54.47	278.75 ± 60.91	0.041

Values are presented as mean ± standard deviation.
ARV, antiretroviral; TDF + 3TC + EFV, tenofovir + lamivudine + efavirenz; AZT + 3TC + EFV, zidovudine + lamivudine + efavirenz; AZT + 3TC + NVP, zidovudine + lamivudine + nevirapine; TDF + 3TC + NVP, tenofovir + lamivudine + nevirapine.

Table 3. Hypersensitivity reactions to antiretroviral, trimethoprim sulfamethoxazole, and antitubercular drugs

Variable	CD4 count					p value
	<50	51–200	201–350	351–499	≥500	
No hypersensitivity	89 (35)	76 (30)	48 (19)	19 (7)	25 (10)	0.104
With hypersensitivity	29 (35)	31 (37)	14 (17)	8 (10)	1 (1)	0.167
HRZE	0 (0)	2 (67)	0 (0)	1 (33)	0 (0)	
Rifampicin/pyrazinamide	2 (67)	1 (33)	0 (0)	0 (0)	0 (0)	
Cotrimoxazole	7 (50)	7 (50)	0 (0)	0 (0)	0 (0)	
Nevirapine	5 (19)	11 (41)	6 (22)	5 (19)	0 (0)	
Efavirenz	5 (50)	3 (30)	1 (10)	1 (10)	0 (0)	
Lamivudine	5 (45)	4 (36)	1 (9)	1 (9)	0 (0)	
TDF + 3TC + EFV	4 (40)	2 (20)	4 (40)	0 (0)	0 (0)	
AZT + 3TC + NVP/AZT + 3TC + EFV	1 (20)	1 (20)	2 (40)	0 (0)	1 (20)	

Values are presented as number (%).
HRZE, isoniazid + rifampicin + pyrazinamide + ethambutol; TDF + 3TC + EFV, tenofovir + lamivudine + efavirenz; AZT + 3TC + EFV, zidovudine + lamivudine + efavirenz; AZT + 3TC + NVP, zidovudine + lamivudine + nevirapine.

Table 4. Drug hypersensitivity reactions and its association with CD4 count

Hypersensitivity syndromes	CD4 count					p value
	<50	51–200	201–350	351–499	≥500	
Hemolytic anemia	4 (36)	4 (36)	2 (18)	1 (9)	0 (0)	
Morbilliform rash	13 (32)	18 (44)	5 (12)	4 (10)	1 (2)	
Erythema multiforme	3 (38)	2 (25)	1 (13)	2 (25)	0 (0)	
Urticaria	1 (17)	3 (50)	2 (33)	0 (0)	0 (0)	
Dyslipidemia	1 (50)	0 (0)	1 (50)	0 (0)	0 (0)	
Serum sickness	3 (60)	1 (20)	1 (20)	0 (0)	0 (0)	0.311
Hepatitis	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
Thrombocytopenia	2 (33)	0 (0)	0 (0)	4 (67)	0 (0)	
Bronchospasm	0 (0)	1 (50)	0 (0)	1 (50)	0 (0)	
Anaphylaxis	0 (0)	1 (50)	0 (0)	1 (50)	0 (0)	
Gynecomastia	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	
SJS	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	

Values are presented as number (%).
SJS, Stevens-Johnson syndrome.

Stevens-Johnson syndrome (SJS). These hypersensitivity reactions occurred across the CD4 groups but was dominantly present in patients with CD4 count of less than 200 cells/mm³. There was no significant difference in the association of CD4 count and the occurrence of the hypersensitivity reactions.

The drug with the most incidence of hypersensitivity reaction was NVP (35%) followed by AZT (17%), cotrimoxazole (13.5%), EFV (13%), and the fixed-dose combination of 3TC + TDF + EFV with 8%. There was a significant difference ($p = 0.001$) in the DHRs caused by the different drugs.

The mean number of days from the intake of the antituberculosis drugs such as INH, HRZE, PZA, and cotrimoxazole to the time of onset of DHRs was <10 days (**Table 5**). Other ARV drugs such as NVP, EFV, 3TC, and AZT + 3TC + EFV had an average of 21–60 days to the onset of DHRs. Other fixed-dose combination ARVs including 3TC + TDF + EFV and AZT + 3TC + NVP had a longer time of onset of DHR with an average of 100–160 days.

Patients with hypersensitivity reactions most presented with rash (38.7%) followed by pruritus (26.8%), dizziness (9.2%), and anemia (6.3%). Other common manifestations include nausea, easy fatiguability, vomiting, gynecomastia, abdominal pain, headache, dyspnea, mood swing, irritability, jaundice, joint pains, and fever.

Table 5. Mean number of days to onset of hypersensitivity reactions from intake of anti-retroviral, trimethoprim sulfamethoxazole, and antitubercular drugs

Medication	Mean ± SD (day)
Isoniazid	6.00 ± 0.98
HRZE	9.00 ± 1.98
Pyrazinamide	10.00 ± 3.21
Cotrimoxazole	12.17 ± 1.45
Nevirapine	21.38 ± 2.67
AZT + 3TC + EFV	47.25 ± 4.89
Efavirenz	53.55 ± 6.78
Lamivudine (AZT)	60.17 ± 7.50
3TC + TDF + EFV	101.00 ± 11.24
AZT + 3TC + NVP	163.00 ± 16.76

HRZE, isoniazid + rifampicin + pyrazinamide + ethambutol; AZT + 3TC + EFV, zidovudine + lamivudine + efavirenz; 3TC + TDF + EFV, lamivudine + tenofovir + efavirenz; AZT + 3TC + NVP, zidovudine + lamivudine + nevirapine.

Among the subjects who had DHRs, seventeen patients needed hospitalization while 66 patients were managed in the out-patient department. All patients had improved status upon discharge and no mortalities were reported. Also, of the patients with DHR, there were 72 patients who had the drugs discontinued and were shifted to other ARV medications. On the other hand, there were 11 patients who continued the drug. Those patients whose ARVs were not shifted were given with an individual preparation of the drug instead of the fixed dose combination ARVs. After shifting the ARVS, only 2 patients had another DHR, specifically to EFV and fixed dose combination 3TC+TDF+EFV. These patients both presented with morbilliform rash.

DISCUSSION

HIV patients showed an increased incidence of drug eruptions when compared to non-HIV individuals [16, 19]. Clinically, hypersensitivity reactions in HIV population are similar than those who are not, being generally manifested as a combination of fever, rash, and internal organ involvement within 6 weeks of drug initiation [20]. The pathophysiology of drug hypersensitivity in HIV patient is multifactorial and are related to changes in drug metabolism, dysregulation of the immune system (immune hyperactivation, patient cytokine profile), oxidative stress, genetic predisposition, and viral factors [13, 21, 22].

The main target of HIV infection is the CD4+ lymphocytes which is a central regulator of the immune system. CD4+ lymphocytes have 2 types such as T helper-1 (Th-1) and -2 (Th-2) which are differentiated by the released cytokines. The Th-1 cells produce interferon gamma (INF-γ) and interleukin (IL)-2 which are important mediators of the cellular immune response, while Th-2 produces IL-4, IL-5, IL-6 and IL-10 which are an important mediator for the humoral immune response that help B lymphocytes produce antibodies [23]. There is immune dysregulation in HIV patients which plays a significant role in the progression of the disease. Whereby, once infected by HIV, changes in cytokine profiles appears specifically increasing the production of IL-4 and IL-5, and decreasing the production of IFN-γ. Early in the course of HIV infection, cytokines produced by Th-1 and Th-2 are in balance. However, as the disease progresses, the production of cytokines by Th-2 such as IL-4 increases and the production of IL-2 cytokine by Th-1 decreases. This shift causes an increase serum level of IgE associated by a reduction in CD4+ T cell count (less than 200 cells/mm^3) [23]. This condition leads to a loss of appropriate immune response [24].

The pathway by which the drugs are presented *in vivo* is still unclear. However, there are 2 hypotheses, the hapten-dependent and hapten-independent (p-i or pharmacologic interaction concept) pathways being proposed [13, 19]. First, the hapten theory states that the culprit drugs or their reactive metabolites are chemically inert but become immunogenic through metabolism to reactive intermediates which then covalently bind or haptenate with endogenous peptides forming an antigenic hapten-carrier complex. The hapten-carrier complex is presented to the human leukocyte antigen (HLA) molecule and then recognized by T-cell receptor (TCR), resulting in the induction of drug-specific cellular or humoral immune responses. The second theory is the hapten-independent or pharmacological interaction with immune receptor (p-i) concept states that the parent drug itself may directly, reversibly, and noncovalently bind to the HLA and/or TCR protein and bypass the classic antigen-processing pathway in antigen-presenting cells [13, 25].

This study revealed a higher incidence of DHR to ARV, antituberculosis, and cotrimoxazole drugs with 25% (83) compared to prior studies [9, 26]. On the other hand, subjects with HIV-TB coinfection had a 26.4% incidence of DHRs. This incidence was similar to a study done by Lehloenya et al. wherein the frequency of DHRs, including those on antituberculosis drugs, had an estimated incidence of 27% [23, 26]. In HIV patients, Vanker and Rhode [22] stated that DHRs occur 100 times more common than the general population. In South, East, and Southeast Asia, the incidence of drug allergy/hypersensitivity among HIV patients ranges from 3%–20% [9]. Currently in the Philippines, there are no published data on the incidence of drug hypersensitivity.

It was observed in this study that DHRs occurred across the different CD4 groups, but the prevalence was not statistically significant (p = 0.104). This result may be explained by the small population of the study and the unequal number of patients across CD4 groups. At present, there is no study that compares the incidence of DHRs among HIV patients across the different CD4 counts. However, in a study by Tatiparthi and Mamo (2015) [27] on the prevalence of ADRs and associated factors of ARV treatment on HIV patients at Jush, they reported that most of the patients with CD4 count between <200-400 cells/mm^3 had 60%–80% of occurrence adverse reactions. Moreover, a prospective study by Bhuvana et al. [28] on the ADRs in HIV patients, it reported a 65.82% incidence of ADRs. However, these previous studies could not be used as comparison since they generally included all ADRs and not merely hypersensitivity reactions.

The results of this study showed that NVP was the most common cause of DHR with an incidence of 35% followed by AZT (17%), then cotrimoxazole (13.5%), then EFV (13%), and the fixed-dose combination of 3TC + TDF + EFV comprising of 8% of patients with DHR. In addition, NVP commonly caused morbilliform rash, seen in 75% of cases (17 of 31). Other reported reactions from NVP included urticaria (4 of 31, 13%), erythema multiforme (3 of 31, 10%), serum sickness (3 of 31, 10%), gynecomastia (2 of 31, 6%), and 1 case each (3%) of SJS and thrombocytopenia. These NVP-associated reactions were observed in patients across the different CD4 groups. It was seen not only in patients with CD4 of less than 200 cells/mm^3 but also in HIV patients with higher CD4 counts. In contrast, a study by Chaponda and Pirmohamed (2011) [29] on the hypersensitivity reactions showed that NVP hypersensitivity reactions occurred in 17%–32% of patients and 13% of these are mild rashes. Severe cutaneous reactions such as drug rash with eosinophilia and systemic symptoms (DRESS) and SJS has also been reported in 0.37% of NVP-associated reactions, and these reactions were also noted to occur in patients with higher CD4 counts [13]. NVP-

induced hypersensitivity was also found to occur in healthy patients receiving the drug for postexposure prophylaxis [30].

AZT, the second drug with the most reported DHR in this study mainly caused anemia in 67% (10 of 15) of patients with AZT-related reactions. The other DHRs included thrombocytopenia (4 of 15, 27%) and morbilliform rash (1 of 15, 6%). This finding was comparable to a study by Chowta et al. (2018) [31], whereby 33% (26 of 79) had reactions to AZT and among these patients, 34% had anemia, 34% had neutropenia, and 31% with thrombocytopenia, although no cutaneous reactions were reported. The drop in the hemoglobin reported in this study was not significant since majority of the patients had a normal to high baseline hemoglobin, hence the decrease was not large enough to cause overt anemia.

In this study, there were 13.5% (12) patients who had hypersensitivity reactions to cotrimoxazole, and all were observed to have cutaneous DHRs. Of these, 8 out of 12 patients were observed to have morbilliform rash. The other reported reactions included urticaria, erythema multiforme, bronchospasm, and anaphylaxis with 1 reported case each. A similar study by Yunihastuti (2014) [8], cutaneous drug reactions were commonly reported in cotrimoxazole, with maculopapular rash being the most reported cutaneous reactions. Other reactions vary from urticaria, eczematous and fixed drug eruptions, erythema multiforme, and severe cases of SJS and TEN [8]. These reactions were observed to occur within 7 days after the initiation of therapy. The incidence of DHR to cotrimoxazole was in contrast with previous studies that reported higher incidence of 40%–80% compared to the 3%–5% in healthy subjects [13, 32].

The hypersensitivity reactions to anti-tuberculosis drugs such as INH, PZA, and RIF were rarely reported in this study. There were only 2 cases of RIF-related hypersensitivity reactions, 1 case of PZA-induced DHR, and 3 cases of INH-induced hypersensitivity reactions. These antituberculosis drugs commonly presented as morbilliform rash. INH caused anaphylaxis and bronchospasm in this study. Previous studies similarly reported that rash was the commonly reported DHR among HIV patients on anti-tuberculosis medications occurring within the 16 weeks of treatment [33-35]. A cross-sectional study in Kenya by Nunn et al. (1992) [36] reported cases of severe cutaneous reactions such as SJS. However, in this study, there was no reported SJS caused by any of the anti-tuberculosis medications.

In this study, the most commonly reported DHRs were morbilliform rash (46.5%) mainly to NVP and EFV, followed by hemolytic anemia (12.5%) from AZT, then erythema multiforme (9.1%), and urticaria and thrombocytopenia with 6.82% each. Such findings were in line with previous studies whereby cutaneous drug reactions were the most common manifestations of drug hypersensitivity [13, 15-16, 31].

It was observed in this study that DHRs occurred in 37% of patients under group 1 (CD4 of 51–200 cells/mm³) followed by group 1 (35%), group 3 (17%), group 4 (8%), and group 5 (1%). However, this study found no association between CD4 count and hypersensitivity reactions to ARV, antituberculosis, and cotrimoxazole drugs ($p = 0.311$). Although previous studies reported that a reduction in CD4 count leads to immune dysregulation predisposing advance HIV patients to DHRs [13, 22, 23], the result of the study may imply that occurrence of DHRs in HIV patients are not solely affected by CD4 count. A similar study by Smith et al. (2005) on the relationship of CD4 count and toxicity profiles of ARV drugs showed that lower CD4 counts were not significantly associated with occurrence of laboratory-defined

hypersensitivity reactions [16, 37, 38]. The findings in this study were in contrast to some studies which have found that those with lower baseline CD4 count were more likely to experience DHRs [4, 39].

Apart from the immunologic mechanisms, other risk factors have been identified that may predispose HIV patients to DHRs which included chemical and drug-related factors, host-related factors, genetics, and concomitant infections [6, 11]. Specifically, the chemical factors and drug administration factors that can predispose patients to DHRs include a large molecular mass, specific immunologic structural moieties, reactive metabolites, parenteral and topical administration, a longer duration of exposure, and frequent repetitive courses of therapy [40, 41].

Host-related factors include gender and older age [6, 37, 40]. In this study, males principally had high incidence of DHRs compared to females. This may be explained by the increased incidence of HIV in homosexual males in the region with a predominant male-to-male sexual transmission. On the contrary, a study by Srikanth et al. (2012) [4] showed that male gender was observed to be a risk factor.

The study of medical genetics in recent years focused on the area of HLA genotypes and their associations with severe drug hypersensitivity. The association with Abacavir-induced hypersensitivity reaction with HLA-B*57:01 was first discovered in 2002. The positive predictive value of HLA-B*57:01 for Abacavir rechallenge hypersensitivity reactions has been reported to be 55% in Caucasians [42, 43]. NVP, meanwhile, has been associated with NVP-induced hypersensitivity or DRESS in patients with HLA-DRB1*01:01 in western Australia, HLA-B*35-05 in Thailand, and HLA-Cw8 in Japan [25].

Additional risk factors include concomitant infections, such that, hypersensitivity reactions may be induced by other pathogens including mycoplasma pneumonia, or viral infections like human herpesvirus-6 (HHV-6) reactivation in patients with DRESS/DIHS (drug-induced hypersensitivity syndrome). HHV-6 reactivation are found to increase T-cell activity after the initiation of the drug eruption and induce the synthesis of proinflammatory cytokines, including tumor necrosis factor-α and IL-6, which may in turn modulate the T-cell-mediated responses [40, 44]. A study by Shiohara and Kano (2007) [45] on the associations between viral infections and drug rashes revealed that aside from HHV-6 reactivation, other herpes virus like HHV-7, Epstein-barr virus, and cytomegalovirus were also found to be coincident with clinical symptoms of DHRs. Chung et al. (2013) [46] also reported that a new variant of coxsackievirus A6 acting as the causative agent provide exogenous peptides for dry presentation and participate in HLA/drug/TCR interactions thereby inducing widespread mucocutaneous blistering reactions mimicking the features of erythema multiform major or severe cutaneous adverse reactions (SCAR). White et al (2015) [47] recently proposed that some patients may acquire primary infections via HHVs or other pathogens that in turn induce drug hypersensitivity. The presence of HHV peptides in patients with high-risk HLA alleles may trigger the activation of cytotoxic T cells, thereby resulting in the development of SCAR [48-50]. The pathogenic factors underlying the unusual presentations of drug hypersensitivity related to viral infections need to be further investigated.

In conclusion, the prevalence of DHRs across the different CD4 groups was not statistically significant (p = 0.104). Also, the analyses found no significant association between the CD4 count and DHRs to ARV (NVP, 3TC, EFV, and fixed-dose combinations of 3TC + TDF + EFV,

AZT + 3TC + NVP, AZT + 3TC + EFV), antituberculosis (INH, RIF, PZA, and fixed-dose HRZE), and cotrimoxazole drugs. Regardless of the baseline CD4 of the patient, the physician should be vigilant in the monitoring of hypersensitivity reactions. Patient education on common DHR to these drugs is very important once the patient has been diagnosed of HIV/AIDS.

The institution had no uniform electronic access to both in- and out-patient records. The records that were gathered were merely based on the outpatient records of the subjects. HIV patients with DHR admitted in the hospital were not included because their records were not included in the outpatient clinic. On top of that, only a few number of patients were included. All these affected the true incidence of all DHR in HIV patients, most specifically the data on DHR to antituberculosis drugs. Furthermore, accuracy of data may have been affected since this was only a retrospective study based on chart review. These resulted to a disparity in the data and underreporting of the true incidence of DHR in this institution. There were no published studies on the incidence of DHR according to Philippine databases such as HERDIN, Philippine Journal of Internal Medicine, and Acta Medica Philippina. This paucity of data on the incidence of DHR in the Philippines and in Asia limited the comparison of the results of the study with other related-studies in the region.

RECOMMENDATIONS

A similar prospective study for 6–18 months duration which would include both in- and out-patient registries is recommended. Also, an ideal sample size should be computed based on the true incidence of DHRs to first-line HAART, trimethoprim sulfamethoxazole, and antitubercular agents.

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