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# Incidence of Allergic Drug Eruption due to Cotrimoxazole in HIV-Positive Individuals with CD4 ≤200 Cells/ul

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**Abstract**

Allergic drug eruptions (ADE) remain a challenge in people living with HIV (PLWH), requiring more studies to guide clinical approaches. While cotrimoxazole is widely used as prophylaxis in PLWH, relationship between client characteristics toward the occurrence of cotrimoxazole ADEs is still poorly understood.

A retrospective cohort study followed PLWH initiated with antiretroviral therapy (ART) in St. Carolus Hospital between January 2009 to December 2021. ADE occurrence due to cotrimoxazole were tested for significance using Pearson's Chi-square and Fisher's Exact Test (significant outcome measured as $p < 0.05$) against CD4 levels at very low (0-100 cells/ul) and low (101-200 cells/ul) groups, comorbidities, and retention status.

Cotrimoxazole-related ADEs occurred in 258 (14%) of 1789 subjects with CD4 levels ≤200 cells/ul. Comorbidities of Hepatitis B, Hepatitis C, and M. tuberculosis infections were found in 11, 4, and 95 subjects respectively. 151 (59%) of ADE group had very low CD4 levels (p value > 0.05). No significant difference was found in ADE incidence between age groups, genders, CD4 levels, comorbidities, and ART retention.

Cotrimoxazole-induced ADE is unrelated to CD4 levels, and ART retention was not affected. ADE severity ranges from mild to serious manifestations, and close monitoring is crucial to ensure ADEs are treated ART are well-maintained.

**Keywords**

HIV, CD4, cotrimoxazole, allergic drug eruption, ARV adherence

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## Introduction

According to the Indonesian Ministry of Health information center, summarized in the HIV/AIDS and Sexually Transmitted Infections Information System, per 2019, the number of HIV-positive cases in Indonesia continued to rise from 2009, and has reached its peak in 2019 with 50,282 new cases. Meanwhile, Acquired Immunodeficiency Syndrome (AIDS) cases had a different trend along those eleven years, having reached its peak in 2013 with 12,214 cases, then began to decline with a total case of 7063 in 2019. This trend needs to be maintained by accelerating new case findings, increasing awareness on the importance of antiretroviral treatment, and if necessary, early prophylactic prevention of certain diseases.[1,2]

AIDS is a condition where CD4 level is below 200 cells/microliter (cells/ul), or if a person has already been infected with opportunistic diseases, which are diseases that occur more often or are more severe in people living with HIV (PLWH).[3] In the prevention of these opportunistic infections (OI), the Indonesian government implement cotrimoxazole (or trimethoprim-sulfamethoxazole, TMP/SMX) prophylaxis guideline for HIV-positive individuals with World Health Organization (WHO) clinical staging of 3 or 4 and/or with

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CD4 levels below 200 cells/μL, including pregnant women. Based on the recommendations of WHO and International Standards for Tuberculosis Care (ISTC), all HIV-positive individuals who have been diagnosed with tuberculosis should also be given cotrimoxazole as prevention regardless of the CD4 count, given at a dose of 800mg/160mg daily while receiving anti-tuberculosis therapy. Cotrimoxazole prophylaxis can be discontinued once the anti-tuberculosis treatment has been completed, and CD4 count has reached >200 cells/μL. The target of this therapy is to lower the incidence of OI such as *pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis in HIV-positive individuals.[1]

Allergic reactions linked to sulfonamide antimicrobials include the entire Gell–Coombs spectrum of hypersensitivity reactions. Type 1 reactions associated with IgE-mediated reactions such as urticaria, angioedema, and anaphylactic shock could occur. People with type 1 hypersensitivity are found to have IgE antibodies toward the parent drug, with the N1 heterocyclic ring as the immunogen recognized by IgE.[4]

Non-type 1 hypersensitivities caused by sulfonamide antimicrobials are believed to be caused by the metabolites of the drug. Sulfonamide antimicrobial agents undergo acetylation, glucuronidation, and hydroxylation to various metabolites. A particular metabolite associated with allergic immunogenicity is the N4-hydroxylated metabolite, which could be oxidized to a reactive nitroso compound. This compound can be reduced through a reaction utilizing glutathione or acetylated using the NAT 2 enzyme. People who have deficiencies in glutathione or are slow-acetylator phenotypes may be predisposed to experience non-type-I hypersensitivity reactions due to decreased ability to metabolize these metabolites. The reactive nitroso compound can bind directly to T-cells to induce maculopapular eruptions, including Stevens-Johnson syndrome.[4,5]

Risk factors associated with greater incidence of cotrimoxazole hypersensitivity in people living with HIV remains poorly understood, although it is found that drug hypersensitivity reactions are 100 times more common in HIV-positive individuals.[6] Several factors could play a role in inducing allergies in people living with HIV which include polypharmacy, slow acetylator status, glutathione deficiency, CD4 <200 cells/ul, latent cytomegalovirus infection, Epstein-Barr virus infection, HHV-6 infection, and high CD8 + cells (> 460 cells/ul).[7-10]

Understanding what are the possible risk factors that increase susceptibility toward allergic reactions is important for health care providers (HCP) in order to provide a more effective and appropriate education for clients. HCPs knowing which characteristic unique to the client that may increase their susceptibility toward allergic reactions would be able to emphasize certain points in the education process and help increase clients' awareness of their condition and how to look for a solution in case anything adverse were to happen. We conduct this study in hopes to shed some light on which client characteristic that may be correlated with a higher incidence of allergic drug eruption due to cotrimoxazole.

## Method

### Ethical Statements

This study was granted ethical approval with reference number 105/KEPPKSTIKSC/X/2022 from the Ethics Commission of Health Research and Development of St. Carolus School of Health Sciences. All data were decoded, and clients' informed consent was not mandatory.

### Study Populations

Client registry and medical records between January 2009 to December 2021 from St. Carolus Hospital, Jakarta, Indonesia, were reviewed retrospectively. Inclusion criteria are HIV-positive individuals initiated with ART in St. Carolus Hospital and tested for CD4 levels prior to ART initiation. Individuals not given cotrimoxazole due to prior allergy history or if records were incomplete were excluded.

### Data Collection

A standardized registry form was used to collect the demographic variables at ART initiation (gender, age), HIV-related variables (risk exposure, ART initiation date, baseline CD4 level, history, and occurrence of cotrimoxazole hypersensitivity, prophylaxis treatment, retention status, comorbidities) from clients' medical records.

Allergic drug eruptions (ADE) due to cotrimoxazole were determined through medical records based on physicians' notes and diagnosis regarding the occurrence of cutaneous manifestations reported by clients through offline and online doctor consultations within 30 days since the first dose, followed by the disappearance of rash after stopping cotrimoxazole.

### Statistical Analysis

Statistical analysis was performed using the SPSS software (version 23.0). Categorical variables were expressed as percentages and numbers. Pearson's Chi-square test was used to analyze correlations between categorical data and ADE incidence with significant outcome measured as $p < 0.05$.

## Results

4865 clients were initiated with ART in St. Carolus Hospital from January 2009 to December 2021. 2123 clients have baseline CD4 levels of ≤200 cells/ul prior to ART initiation and were screened for cotrimoxazole prophylaxis eligibility. 1789 subjects who were given 800/160mg TMP/SMX daily were included in the study, while 334 clients who did not receive cotrimoxazole prophylaxis with CD4 levels ≤200 cells/ul were excluded due to prior history of cotrimoxazole hypersensitivity and/or other personal reasons (refused treatment, etc). Out of 1789 subjects, 258 (14%) developed ADEs (151

**Table 1.** PLWH Characteristics with Incidence of ADE.

| Characteristics of PLWH at ART Initiation | PLWH with ADE due to TMP/SMX (n = 258) | | PLWH without ADE (n = 1531) | | | |
|---|---|---|---|---|---|---|
| | n | % | n | % | Total | *p* value |
| Age of ART Initiation | | | | | | 0.82 |
| < 20 years old | 4 | 18% | 18 | 82% | 22 | |
| 20–45 years old | 230 | 14% | 1381 | 86% | 1611 | |
| > 45 years old | 24 | 15% | 132 | 85% | 156 | |
| Gender | | | | | | 0.21 |
| Male | 232 | 14% | 1403 | 86% | 1635 | |
| Female | 26 | 17% | 128 | 83% | 154 | |
| Exposure | | | | | | 0.37 |
| Vaginal Sex | 51 | 15% | 300 | 85% | 351 (20%) | |
| Anal Sex | 188 | 15% | 1069 | 85% | 1257 (70%) | |
| Perinatal | 18 | 13% | 122 | 87% | 140 (8%) | |
| Blood Transfusion | 0 | 0% | 3 | 100% | 3 (0.2%) | |
| People who Inject Drugs | 1 | 33% | 2 | 67% | 3 (0.2%) | |
| Others | 0 | 0% | 35 | 100% | 35 (2%) | |
| Baseline CD4 | | | | | | 0.489 |
| 0–100 | 151 | 14% | 891 | 86% | 1042 | |
| 101–200 | 107 | 14% | 640 | 86% | 747 | |
| ART Retention ≥3 months since ART Initiation | | | | | | 0.07 |
| Still on ART | 234 | 15% | 1325 | 85% | 1559 | |
| Lost to follow up | 24 | 10% | 206 | 90% | 230 | |

(59%) had baseline CD4 levels of 0–100 cells/ul, 107 (41%) had baseline CD4 of 101–200 cells/ul). Subjects' characteristics are shown in Table 1.

Using the Pearson Chi-square and Fisher's Exact test, out of 1789 subjects given cotrimoxazole compared to their baseline CD4 levels, those who developed ADEs in the CD4 levels of 0–100 cells/ul group (n = 151) and CD4 levels of 101–200 cells/ul (n = 107) was found to be insignificant ($p > 0.05$).

## Discussion

Adverse drug reactions in the form of ADE remain a challenge in people living with HIV. The complexities of polypharmacy, drug interactions and overlapping clinical manifestation of drugs' side effects and OIs faced by vulnerable clients necessitate the need for more data to support consideration in clinical approaches. Higher risk of drug hypersensitivity in people living with HIV suggests a higher occurrence of sulfanil-amide-related side effect in HIV-positive individuals. Cotrimoxazole was widely used in prevention and treatment of OI in people living with HIV. The prevalence of rash is higher than in the general population.[11] Although this study was done with 1789 subjects from the clinic with the largest number of HIV-positive clients on treatment in the national level, study population was taken from a single HIV primary care provider, and therefore a direct generalization should not be made at a national or global level. Several studies on the relationship between CD4 levels toward the occurrence of cotrimoxazole ADEs in clients with <200 cells/ul CD4 counts showed that lower CD4 levels are associated with higher propensity for the occurrence of ADEs.[7,12]

### *Age, Gender, Risk Exposure*

Multiple factors are related with drug hypersensitivity reactions including drug-related factors, host-related factors, and concomitant illness.[13] Age, gender and risk exposures are part of host-related factors of this study. Symptoms and drugs involved in ADEs might vary according to age.[14] In this study, no significant differences were found regarding the incidence of cotrimoxazole allergy between different age groups. Similar findings were found in previous study of people living with HIV receiving cotrimoxazole perhaps due to the study population, where clients in the productive age range (20-45 years old) contribute 90% of the allergy group.[15]

Most of the subjects who experienced ADEs in this study are male (232 of 258 subjects, 90%). Comparing between genders, 17% of female subjects (26 females with ADE/154 females who were given cotrimoxazole), and 14% of male subjects (232 males with ADE/1635 males who were given cotrimoxazole) are found to experience ADE when given cotrimoxazole ($p > 0.05$). Previous studies found that females have higher risk of drug allergy.[13,14] The higher adverse event rate in females has been linked to differences in pharmacokinetic factors, hormonal factors, and higher tendency of symptom reporting.[16-18] Comparison between both genders in our study is not statistically significant, perhaps due to having a predominantly male client population in the HIV clinic.

**Table 2.** PLWH with Coinfections Compared to Incidence of ADE.

| | PLWH with ADE due to TMP/SMX | | PLWH without ADE to TMP/SMX | | Total | *p value* |
|---|---|---|---|---|---|---|
| History of Hepatitis at ART Initiation | | | | | | |
| Hepatitis B | 11 | 15% | 60 | 85% | 71 | 0.45 |
| Hepatitis C | 4 | 11% | 32 | 89% | 36 | 0.39 |
| Tuberculosis Diagnosis at ART Initiation | 95 | 15% | 530 | 85% | 625 | 0.27 |

Risk exposures recorded are unsafe anal intercourse (1257, 70%), vaginal intercourse (351 subjects, 20%), perinatal transmission (140 subjects, 8%), blood transfusion (3 subjects, 0.2%), people who inject drugs (3 subjects, 0.2%), and others (35 subjects, 2%), although there is not significant difference between the ADE group and the non-ADE group ($p > 0.05$) (Table 1).

## Comorbidities

The current understanding of increased drug hypersensitivity in HIV remains unclear. Studies stated some likely contributors are genetic risk, increased oxidative stress, depletion of immunoregulatory cells and consumption of protective antioxidant molecules.[19] Other studies also stated that several age-related morbidities occur at earlier ages in individuals.[20] HIV, aging, and inflammation caused by other comorbidities contributes to the immunology process that affected the occurrence of drug hypersensitivity in people living with HIV.[21] The occurrence of ADE was also not significantly related to the presence of these illnesses when compared to ADE occurrence with co-infection (HBV, HCV, TB each have a $p$ *value* $> 0.05$), (Table 2).

Additionally, our descriptive findings show that a higher percentage of clients with comorbidities around their ART initiation period are in the lower CD4 group; 58% of Hepatitis B (HBV) infected clients, 61% of Hepatitis C (HCV) infected clients, and 81% of *M. tuberculosis* (TB) infected clients have ≤100 cells/ul (Table 3). Further analysis such as the onset and severity of the ADE, medication history, inclusion of people living with HIV with baseline CD4 > 200 cells/ul, and other medical history might affect these findings.

## Cotrimoxazole Related ADE and ART Retention

Adherence of ART is an important factor that contributes to treatment effectiveness for people living with HIV. In a recent Ethiopian study, 10% of clients discontinued ART because of cotrimoxazole allergy.[22] Various conditions affect client's decision to retain in treatment such as service-related constraints and personal desire to resume a productive life.[23] Research shows that health literacy is significantly associated with better retention in care.[24] HCPs are the main source of health information for these clients; thus, it is imperative that clients are educated on their medical condition. In our study, several clients communicated with their HCPs regarding their hesitancy to continue ART due to suspicion that the allergic

**Table 3.** PLWH with Coinfections Diagnosed at ART Initiation Compared to CD4 Baseline Levels.

| | CD4 0–100 cells/ul | | CD4 101–200 cells/ul | | |
|---|---|---|---|---|---|
| Coinfections at ART Initiation | n | % | n | % | Total |
| Hepatitis B | 41 | 58% | 30 | 42% | 71 |
| Hepatitis C | 22 | 61% | 14 | 39% | 36 |
| Tuberculosis | 509 | 81% | 116 | 19% | 625 |

symptoms were associated with ART instead of cotrimoxazole. However, with proper education, our study showed no significant difference ($p > 0.05$) between loss-to-follow-up clients with ADE (24/258 subjects, 9%) and without ADE (206/1531 subjects, 13%) toward cotrimoxazole in our clinic. This shows that clients understood the importance of maintaining ART despite experiencing allergy. Same day ART initiation is implemented should there be no contraindications, and the necessary education regarding the possibility of a cotrimoxazole allergy is emphasized to encourage clients to report their symptoms. Every newly-diagnosed people living with HIV will be registered to the clinic's reminder system through online message notification. Clients could also send their queries to the clinic's online messaging service, where in-charge clinic staff will reply and recommend clients to come to the clinic if they are presented with alarming symptoms including ADEs for further on-site assessment.

## Low and Very low CD4 Level and ADE

HIV infection is associated with immune deregulations and higher rates of coinfections and reactivation of certain viruses, thus increasing conditions requiring drug administration. It has been found that the frequency of drug hypersensitivity reactions (DHR) in people living with HIV is particularly high.[25] HIV infection directly (through active viral infection, immune dysregulation/stimulation) or indirectly (through nutritional deficiencies, associated infections/diseases, multiple skin diseases, multiple drug use, or increased exposure to high-risk medication such as cotrimoxazole) would seem to be a causative cofactor for severe cutaneous ADE.[10,26] HIV appears to enhance drug reactivity in general, not only for specific drugs.[8] HIV itself leads to a decrease and eventual loss of function of T cells in the blood and skin, in addition to dysregulation

of tolerance to self-antigens.[26] Incidence of severe DHR in people living with HIV has also been reported to increase as the disease progresses, such as decreasing CD4 + T cells counts and CD4/CD8 ratio, and expression of HIV-1 viral protein Tat (HIV-specific protein essential for the viral replications).[12,27-29]

In our study, 258 subjects (14%) of 1789 clients with CD4 <200 cells/ul experienced ADEs related to cotrimoxazole. Bivariate analysis using the Fisher's Exact Test showed insignificant relationship between the incidence of allergy to CD4 levels. No significant difference of ADE incidence was found between very low CD4 (0-100 cells/ul) group (n = 151) and low CD4 group (101-200 cells/ul) (n = 107) ($p > 0.05$). A similar finding was found in a 1 year study of 319 subjects that showed that CD4 < 100 had an unsignificant role as risk factor of cotrimoxazole ADE, while dose of cotrimoxazole was a significant risk factor (OR = 12,7; p = 0.01).[30] Other study also found no correlation between CD4 level and and EFV-related rash in 1212 subjects in a 13-year retrospective cohort study in Indonesia, and no significant correlation between 307 HIV-TB adults' CD4 level and TB treatment allergy.[31,32]

Other than CD4 level, studies found at least three distinct processes contribute to cotrimoxazole ADE: (1) production of reactive metabolites via drug metabolism/bioactivation; (2) reactive oxygen species (ROS) processing, and (3) binding of reactive metabolites to proteins/DNA, resulting in inflammation, cell damage, neo-antigen formation, and immune response.[19] A study of 12 toxic epidermal necrosis (TEN) cases in HIV-positive individuals found that not the level of CD4 alone but the ratio of CD8 to CD4 was significantly related to TEN occurrence (p = 0.006).[33]

People living with HIV and especially those with progressive diseases have increased susceptibility to oxidative stress, which has been proposed to increase exposure to toxic drug metabolites and potentially cause immune mediated ADEs.[19] Glutathione, a cellular antioxidant responsible for detoxifying toxic reactive metabolites such as sulfamethoxazole-nitroso (SMX-NO) and preventing tissue damage is found to be significantly lower in people living with HIV.[34,35] This results in a higher risk of SMX-induced hypersensitivity reactions in HIV-positive individuals than in HIV-negative people. The expression of the HIV Tat as the diseases progresses is also found to be significantly increased cellular sensitivity to reactive drug metabolites and significantly decreased intracellular GSH concentration.[28] The Tat protein would be secreted by infected cells, in relation to the viral load and disease progression, and promotes drug reactions, increasing oxidation status.[36]

One of the limitations of this study is the lack of Naranjo scoring or other standardized scoring to ascertain allergic reaction, due to the study being done retrospectively, thus defining allergy depended on medical record diagnoses from several HCPs that stated the presence of newfound rash post-cotrimoxazole ingestion, and having the rash disappear as cotrimoxazole was stopped. This could lead to an underdiagnosis, especially when it is affected by the variety of clients' tolerance toward drug allergy manifestations, where allergy case findings depended on clients' awareness of the symptoms.

## Conclusion

Allergic drug eruptions due to cotrimoxazole or TMP/SMX is unrelated to CD4 level in 1789 people living with HIV presented with CD4 level <200 cells/ul prior to ART initiation in St. Carolus Hospital. ART retention remains high (>90%) in clients with ADEs. Age, gender, exposure risks, and comorbidities presented on ART initiation does not affect cotrimoxazole hypersensitivity in our study. While ADE severity ranges from mild to serious complications, close monitoring and data reporting should be done in HIV clinics to ensure clients are diagnosed and treated on-time. Healthcare providers in the clinic need to be aware of clients' discomfort, and clear communication during close monitoring is imperative through client-centered care.

Healthcare providers need to make sure that clients and their partners, family or caregivers are aware and able to inform HCP of any signs of ADE, and that cotrimoxazole can be one of the most common causes of drug-induced ADE or any other allergic manifestations. Comprehensive explanations are important prior to the initiation of any medication, despite any CD4 level. The importance of ART retention to allow for the improvement of patients' conditions should be discussed early in the ARV initiation process to assure patients that even though treatment may induce certain allergy or side effects, such circumstances can be minimized by prompt healthcare attention. Further research involving more variables such as family history, genetics, nutritional status, medications, co-infections, antioxidant status, severity of ADE, and manifestations of ADE could be observed if resources are available. However, in a low-resource setting, accessible markers to predict the incidence of ADEs in people living with HIV could be useful for future studies, perhaps a more detailed record regarding the type of allergic drug eruption should be encouraged, as certain additional manifestations such as fever, gastrointestinal symptoms, etc could mark a more severe allergic reaction and thus be of significant information for future analysis.

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