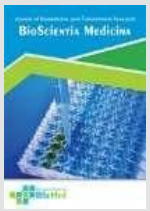
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Allergy on HIV Infections: A Narrative Literature Review

Muhammad Iqbal Andreas[1], Dwitya Elvira[1*], Raveinal[1]

[1]Division of Allergy and Immunology, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

ARTICLE INFO

Keywords:
Allergy
HIV
Immunoglobulin E
T-helper 1
T-helper 2

***Corresponding author:**
Dwitya Elvira

E-mail address:
dwitya.elvira.de@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v7i2.771

A B S T R A C T

HIV infection causes not only immune insufficiency but also immune dysregulation. Following HIV infection, cytokine profiles change, with a production of IL-4 rising along with IL-5 and a decrease in INF-γ. This literature review aimed to describe allergy on HIV infection. At the initial phase after infection, cytokines produced by Th1 and Th2 are balanced, but later as the infection progresses, cytokines produced by Th2 will rise, while cytokines produced by Th1 will fall. Elevation of IL-4 will make B cells produce more IgE. Patients with even lower CD4 still have this allergic phenomenon caused by IgE. Allergic manifestations of HIV include rhinitis, asthma, adverse cutaneous drug reactions (ACDR), immune reconstitution inflammatory syndrome, hyperallergic state (IRIS), and atopic dermatitis. In conclusion, it is important to consider allergic manifestations even in AIDS patients, especially incidents of ACDR and IRIS, which can be life-threatening.

1. Introduction

Allergies are caused by an overreaction of the immune system to normally harmless substances, such as pollen or certain foods.[1,2] HIV (human immunodeficiency virus) is a virus that attacks the immune system, specifically the CD4 T-cells, which are important for the proper functioning of the immune system. In people living with HIV, the immune system may be weakened, making them more susceptible to infections and certain types of cancer.[3] In allergic patients, there is a change in the balance between T-helper 1 (Th1) and T-helper 2 (Th2). The same condition also appears in HIV patients.[1] Hypersensitivity, and allergic manifestations have been observed in HIV patients. Drug hypersensitivity is the most common reaction, followed by rhinitis and pruritus. A previous study found an increase in allergic manifestations such as asthma in HIV patients by 15.5% compared to patients without HIV.[4] The occurrence of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) increased compared to normal populations.[2] This literature review aimed to describe allergy on HIV infection.

Mechanism of allergy on HIV

CD4 lymphocytes are important regulators of the body's immune system, which can proliferate and differentiate, developing into several subsets, including Th1 and Th2. Th1 produces interferon gamma (INF-γ) and interleukin 2 (IL-2), which are important mediators of cellular immune responses. Th-2 produces IL-4, IL-5, IL-6, and IL-10, which play

an important role as mediators of the humoral immune response and help B lymphocytes produce antibodies.[3] In the later stages of HIV infection, cytokines production by Th1 cells would decrease, and Th2 cells increase the production of IL-4, IL-5, and IL-13. The increased production of IL-4 encourages B cells to increase IgE production.[4]

Another study stated that cells infected with HIV are more susceptible to cell damage and death, such as from drug metabolites. Further damage to this cell is then translated as a danger signal, stimulating T lymphocytes to release cytokines that will cause a hypersensitivity reaction. Glutathione deficiency has also been suggested as a mechanism that can cause this reaction. Other studies show that the Tat protein stimulates HIV replication. The expression of the Tat protein is correlated with increased oxidative stress, decreased biosynthesis, and cellular concentration.[3] A previous study found that HIV/AIDS patients still showed increased production of allergen-specific IgE despite having a low CD4 count.[5] Based on these findings, AIDS patients can still produce allergen-specific IgE antibodies, which can increase upon exposure to allergens and are not affected by CD4 cell levels.[6]

Manifestation of allergy on HIV

Rhinitis and sinusitis

Rhinosinusitis has been reported in up to 68% of patients with HIV. Marth et al. also found that most HIV patients (73%) have acute allergic rhinitis. In 81% of patients, dust or house mites are known allergens, and pollen is in 63% of patients. A study showed an increase in Th2 in HIV patients induced the secretion of IL-4, IL-5, and IL-13. An increase in IL-8 was also found during an inflammatory reaction after being provoked by an allergen. If possible, perform a prick test to determine the allergen. The skin-prick test is a sensitive and cheaper method to confirm an allergen compared to the measurement of IgE.[7]

Treatment in cases of rhinitis and sinusitis in HIV patients is no different from that in other patients. Avoiding exposure to allergens indoors and outdoors is very important to control the recurrence of symptoms. Oral antihistamines and decongestants can be given in cases of rhinitis. These drugs can be given together with a nasal spray to reduce symptoms. In co-infection conditions with bacteria, broad-spectrum oral antibiotics can be given, such as amoxicillin (regular or high dose), amoxicillin/clavulanate (regular or high dose), telithromycin, or cefuroxime.[7]

Asthma

The causes of asthma in HIV patients are the same as in non-HIV patients, but some mechanisms occur only in HIV patients. HIV infection can potentially cause lung damage through activation of the immune system, inflammatory processes, direct effect of HIV proteins, and activation of memory cells CD4. Several studies have found that a higher viral load is related to worsening lung function.[8,9] Antiretrovirals can also potentially cause an autoimmune or immune reconstitution-like reaction against the lung.

Many studies find an increase in hyperresponsiveness in HIV patients with asthma compared with controls. HIV is known to cause infiltration of CD8 cells into the interstitium and alveoli and is accompanied by a decrease in CD4 cells; this effect is most pronounced in early infection. Recent studies also show that pneumocystis can phenocopy other aeroallergens, such as dust mites. This can cause increased activation of goblet cells, mucus production, eosinophilic perivascular inflammation, allergic inflammation, and airway resistance.[10]

Many factors contribute to asthma in HIV patients. It is estimated that current therapy cannot be effective in HIV patients. In addition, the possible role of antiretroviral therapy (ART) in this mechanism could also affect this effectiveness. Other complications from inhaled corticosteroids, such as candidiasis, tuberculosis, and pneumonia, are also at risk. Pharmacological studies and case reports also found that the combination of ritonavir and fluticasone could cause Cushing syndrome and adrenal insufficiency,

and the combination of them is contraindicated in HIV patients (ritonavir increases serum level of fluticasone). Further study is needed for asthma therapy in HIV patients.[9,10]

Adverse cutaneous drug reaction (ACDR)

Hypersensitivity to the drug is 100 times more common in HIV patients. AIDS is 1000 times more likely to cause Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) than the general population. These cases have the same mortality rate as the general population, approximately 5 to 30%. The most common symptoms are fever, rash on the skin, and internal organ symptoms, which usually occur within 4-6 weeks after using drugs but can also occur in one week. An increased incidence of hypersensitivity to drugs or drug eruptions occurs due to dysregulation of the immune system, which is vulnerable to oxidative stress.[11]

Most of the reactions to this drug are due to trimethoprim-sulfamethoxazole (TMP/SMX), which occurred in 75% of all reported cases. An increase in allergic reactions from 2-8% in the general population to 43% in HIV patients and 69% in AIDS patients. Factors contributing to increased drug reactions in HIV patients are polypharmacy, slow acetylator status, relative glutathione deficiency, CD4 T cells less than 200 cells/mm^3, latent infection of cytomegalovirus and Epstein-Barr, and CD8 T cells more than 460 cell/mm^3.[12]

Typical symptoms are maculopapular erythema or a morbilliform rash with constitutional symptoms such as fever, myalgia, and chills. A morbilliform rash occurs in 95% of drug reactions. A rash appears itchy, symmetrical, and erythematous and usually appears on the legs and skin folds but not on the face. Life-threatening symptoms are confluent erythema, palpable purpura, skin blisters, skin necrosis, and mucosal erosion; urticaria, a swollen tongue, dyspnea, wheezing, and hypotension; a temperature over 40^0C, enlarged lymph nodes, arthralgia or arthritis, eosinophilia >1000/μL, lymphocytosis with atypical and elevated liver enzyme levels.[12]

Trimethoprim-sulfamethoxazole (TMP-SMX) uses as a prophylactic therapy in pneumonia due to Pneumocystis jirovecii could cause hypersensitivity reactions such as rash, fever, hematological disorders, transaminase disorders, and anaphylaxis to SJS-TEN. Allergic reactions range from 44% to 83% in patients with HIV but less than 10% in the average population. A hypothesis behind increased allergic reaction is systemic glutathione deficiency that increases toxin derivatives such as hydroxylamine, which will cause allergy. [12] A study found that cutaneous drug reactions occurred in 47.6% of patients, generally within two weeks of therapy, with a daily dose of more than 16 mg/kg TMP/SMX and an age more than 34 years. A gene mutation was also found to be associated with hypersensitivity SMX.[12]

Fifty to sixty percent of patients with TMP/SMX experience a morbilliform rash and fever within 1-2 weeks after therapy, but severe symptoms may persist. The drug can be continued in a mild condition and accompanied by symptomatic treatment such as systemic antihistamines and topical corticosteroids. Periodic assessment and patient education on life-threatening symptoms are needed. If the rash persists, doses of TMP/SMX need to be decreased. If the symptoms persist, oral corticosteroids can be administered at a dose of 0.5 mg/kg for a maximum of 21 days. Rechallenge may be performed in symptomatic patients with non-life-threatening hypersensitivity. Desensitization can be done in patients with mild hypersensitivity that is not life-threatening and is known to induce tolerance in 63% of cases. But, of course, this must be done at the tertiary facility.[12]

Acute cutaneous drug reaction: anti-tuberculosis

Skin hypersensitivity is the most common symptom found in HIV (64%). This reaction appeared within eight weeks after administering anti-tuberculosis drugs (ATD). In this study, the patient develops an allergy after consuming OAT 4FDC; reddish spots appear on the whole body, followed by itching and shortness of breath after one week of

taking the drug. After the separate administration of ATD, the patient is known to have an allergy to rifampicin and pyrazinamide. In combination therapy, it is difficult to know the culprit drug; however, rifampicin was reported as the common drug to illicit allergy.[3]

A morbilliform rash is the most common reaction due to the anti-tuberculosis drug. A morbilliform rash occurs in 95% of cases and occurs within 7-14 days after the start of therapy. This morbilliform rash can lead to more severe reactions such as SJS/TEN. Drug hypersensitivity syndrome (DiHS), also known as drug reaction with eosinophilia and systemic symptoms (DRESS), can also occur and cause death. SJS/TEN has a significant mortality rate and is observed after the administration of rifampicin, pyrazinamide, isoniazid, ethambutol, streptomycin, cycloserine, and fluoroquinolones. A study found that all first-line anti-TB therapy can potentially cause an ACDR; co-infection with HIV is a significant risk factor for these cases. Therefore it is advisable to do a rechallenge test by giving a drug that is least likely to cause a reaction first and then monitoring the reactions.[13]

Acute cutaneous drug reaction: antiretroviral

Abacavir (ABC) and nevirapine (NVP) potentially cause hypersensitivity reactions that need special attention. ABC has a fatal risk of up to 8% in patients, with symptoms such as high fever, diffuse lesions (70%), malaise, nausea, headache, myalgia, vomiting, diarrhea, back pain, and arthralgia.[13] Hypersensitivity to ABC commonly appears between days 9-11 of therapy. This case is common in the Caucasian race, patients who recently got treatment with high CD8 values at baseline administration and have positive HLA-B5701. HLA allele B5701 is the dominant risk factor for ABC hypersensitivity, with more than 70% positive predictive value and 95-98% negative predictive value. Initial screening of this allele before administration of the current ABC is recommended. If a reaction to this drug appears, ABC should be discontinued immediately, and this drug should not be given to this patient again.[14]

Skin rash occurs in 15% of patients who receive NVP, and 1.5% have severe symptoms. Hypersensitivity syndrome due to NVP can occur without the appearance of a skin rash but produce systemic symptoms such as fever, myalgia, arthralgia, hepatitis, and eosinophilia. A hypersensitivity reaction occurs early in therapy and rarely occurs after 12 weeks. Risk factors are women, Chinese, high CD4 counts, and low HIV RNA when NVP is given. Maculopapular rash and erythema usually appear on the arms and legs within 2 - 4 weeks of therapy.[14] NVP should be given at 200 mg once daily for the first two weeks and then 2x200 mg to prevent rash. If the rash appears in the first two weeks, the drug should be delayed until the rash heals.[15]

Immune reconstitution inflammatory syndrome and hyperallergic state

Immune reconstitution inflammatory syndrome (IRIS) is a paradoxical form of exacerbation of opportunistic infection or other pathological conditions that usually occurs within the first few weeks (rarely months) of antiretroviral therapy administration. Exacerbation conditions can occur either with an opportunistic infection being treated concomitantly or with previously unrecognized opportunistic infections. T cell-mediated cytotoxicity is thought to play a role in IRIS. This syndrome is a form of exaggerated immune system activation in response to infectious opportunistic pathogens.[14]

A previous study found the incidence of IRIS was estimated at 13% to 16% in patients starting ART. IRIS incidence on previously diagnosed AIDS-related illnesses was 6.4% in Kaposi's sarcoma, 12.2% in herpes zoster, 15.7% in tuberculosis, 16.7% in progressive multifocal leukoencephalopathy, 19.5% in meningitis cryptococcal, and 37.7% in cytomegalovirus retinitis. A low level of CD4 (typically less than 50 cells/μL) when starting ART is also a significant risk factor for IRIS, regardless of whether an opportunistic infection existed. The IRIS mortality rate is approximately 4.5%, which varies by disease comorbidities, ranging from 2.5% in patients with

tuberculosis to 20.8% in cryptococcal meningitis. The most significant cause of death in IRIS is opportunistic infections in the central nervous system.[14,15]

The treatment of IRIS focuses on symptom control. HAART administration can be continued unless there is evidence of severe toxicity due to HAART or IRIS-involving the nervous system. The current guideline recommends HAART administration after two weeks of diagnosis and treatment of opportunistic infections. However, there are special considerations for opportunistic infections involving the central nervous system (e.g., cryptococcal or tuberculous meningitis). HAART may be delayed due to a potentially fatal risk to the central nervous system.[16]

Supportive therapy also includes fluids, electrolyte correction, and optimizing nutritional status. Mild symptoms of IRIS, such as fever and pain, can be treated with paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs). Patients with severe lung disease causing acute hypoxic respiratory failure (pneumonitis secondary to *Pneumocystis jirovecii*) and central nervous system diseases such as Cryptococcus can be given steroids. Biological agents such as a TNF-alpha antagonist may be given in patients with IRIS in the central nervous system resistant to steroids. Patients with the IRIS cytomegalovirus can be given intraocular steroids.[16]

Atopic dermatitis

Atopic dermatitis is characterized by scaly erythematous plaques and is accompanied by itching and often accompanied by lichenification secondary to excoriation and secondary bacterial infection. There is inconclusive data regarding the prevalence of atopic dermatitis in HIV patients. Numerous case studies regarding atopic dermatitis in HIV are still diverse. This fact is possible because there are unclear criteria regarding the diagnosis of atopic dermatitis and many conditions that may mimic atopic dermatitis in HIV patients (including seborrheic dermatitis, papular pruritic eruptions in HIV infection, eosinophilic folliculitis, and papular urticaria). Patients with HIV may have dehydrated skin compared to non-HIV patients, which will decrease skin barrier function.[11] Staphylococcus colonies are often found in atopic dermatitis patients, so it's reasonable to give antibiotics against Staphylococcus. In a recurring case, initiation of phototherapy may be considered to avoid long-term corticosteroid administration.[14]

2. Conclusion

Immune dysregulation due to HIV infection could lead to an allergic reaction. Several allergic reactions range from mild symptoms to life-threatening. It's important to consider allergic manifestations, especially among drugs routinely used in HIV.

3. References

1. Devereux G, Matsui EC, Burney PGJ. Epidemiology of asthma and allergic airway diseases. In: Middleton's allergy principles and practice. Philadelphia: Saunders, 2014: 754–78.
2. Avila PC, Kishiyama JL. Allergic manifestations in AIDS. AIDS allergy and rheumatology. Totowa, NJ: Humana Press. 1997: 77–93.
3. Minhajat R, Djaharuddin I, Halim R, Benyamin AF, Bakri S. Drugs hypersensitivity reaction in patient with human immunodeficiency virus (HIV) Infection. J Allergy Ther. 2017; 8: 252.
4. Becker Y. The changes in the T helper 1 (Th1) and T helper 2 (Th2) cytokine balance during HIV-1 infection are indicative of an allergic response to viral proteins that may be reversed by Th2 cytokine inhibitors and immune response modifiers – A review and hypothesis. Virus Genes. 2004; 28: 5–18.
5. Clerici M, Shearer GM. The T helper cell shift in AIDS: Significance for pharmacotherapy. Clin Immunother. 1995; 3: 95–101.
6. Marth K, Wollmann E, Gallerano D, Ndlovu P, Makupe I, Valenta R, et al. Persistence of IgE-associated allergy and allergen-specific IgE despite CD4+ T cell loss in AIDS. PLoS ONE. 2014; 9: e97893.

7. Shah AR, Hairston JA, Tami TA. Sinusitis in HIV: Microbiology and therapy. Curr Allergy Asthma Rep. 2005; 5: 495.
8. Kirenga BJ, Mugenyi L, De Jong C, Lucian Davis J, Katagira W, Van der Molen T, et al. The impact of HIV on the prevalence of asthma in Uganda: a general population survey. Respir Res. 2018; 19: 1-9.
9. Gingo M, Puri A, Morris A. Asthma in HIV-infected population: A review of respiratory symptoms, pulmonary function abnormalities and pathophysiology. Epidemiol. 2014; 4: 1-8.
10. Adrish M, Gomez GR, Rodriguez EC, Mantri N. Influence of HIV status on the management of acute asthma exacerbations. BMJ Open Respir Res. 2019; 6: e000472.
11. Vanker A, Rhode D. Human immunodeficiency virus and allergic disease. Curr Allergy Clin Immunol. 2009; 22: 168–72.
12. Hoosen K, Mosam A, Dlova NC, Grayson W. An update on adverse cutaneous drug reactions in HIV/AIDS. Dermatopathology. 2019; 6: 111–25.
13. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med. 2008; 359: 2233–44.
14. Siberry GK, Paul ME, Shearer WT. HIV infection and allergic disease. In: Middleton's allergy: Principles and practice. Philadelphia: Elsevier, 2020: 1168–80.
15. Davis CM, Shearer WT. Diagnosis and management of HIV drug hypersensitivity. J Allergy Clin Immunol. 2008; 121: 826-32.
16. Thapa S, Shrestha U. Immune reconstitution inflammatory syndrome. StatPearls. 2022.