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Review Article

Residual immune dysregulation in human immunodeficiency virus infection: implications for hypersensitivity

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ABSTRACT

Residual immune dysregulation persists in people living with human immunodeficiency virus (PLWHIV) despite antiretroviral therapy (ART), characterized by chronic immune activation and imbalances in immune responses that increase the risk of allergic conditions such as drug hypersensitivity, atopic dermatitis (AD), and asthma. This literature review explores the mechanisms underlying immune dysregulation in PLWHIV and its implications for hypersensitivity reactions. HIV infection shifts the immune response from Th1 to Th2, increasing cytokine production, particularly IL-4 and IL-13, and elevating IgE levels, contributing to allergic reactions. Drug hypersensitivity, especially to nevirapine and abacavir, occurs more frequently in PLWHIV, with a higher risk of severe conditions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The management of allergies in PLWHIV remains challenging due to persistent immune dysregulation, limited therapeutic options, and the lack of specific clinical guidelines. Understanding these immunological changes is crucial for developing better strategies for allergy prevention and management in this population.

Keywords: HIV, Immune dysregulation, Hypersensitivity, Allergy, Antiretroviral therapy

INTRODUCTION

The phenomenon of residual immune dysregulation occurs in HIV patients (PLWHIV) with suboptimal CD4+ T cell recovery, characterized by immune activation, inflammation, and coagulopathy. Although ART successfully suppresses the virus, this phenomenon persists, leading to increased inflammatory cytokines, lymphoid tissue damage, and T cell dysfunction, which can impair immune regulation and enhance allergic responses.[1] The depletion or reduction of CD4+ T cells alters the balance between T-helper 1 (Th1) immune responses, which combat infections, and T-helper 2 (Th2) responses, which are associated with allergic reactions. HIV tends to induce a dominant Th1 response while suppressing the Th2 response. One of the most clinically relevant effector responses is hypersensitivity immunity. The Th2 response to allergens, mediated by IL-4/IL-13, IL-5, and IL-13, plays a role in IgE isotype switching and eosinophil recruitment.[2,3]

HIV is a virus that attacks the immune system, particularly CD4+ T cells, affecting both their quantity and function, especially activated CD4+ T cells. The loss of CD4+ T cells can lead to opportunistic infections (OIs), non-AIDS-defining events (nADEs), and mortality in individuals who progress to acquired immune deficiency syndrome (AIDS). As the disease progresses in PLWHIV, HIV

infection can drive higher levels of immune activation and inflammation, both of which are characteristic of the body's ongoing battle against the virus.[5] HIV-1 and HIV-2 share similarities in genetics, transmission, and replication; however, HIV-2 is less transmissible and rarely progresses to AIDS. HIV-1 leads to extensive CD4+ depletion, severe immunodeficiency, and chronic inflammation. Although ART suppresses viral replication, HIV-1 remains associated with metabolic dysregulation, heightened inflammatory responses, and altered gene expression.[4,6,7]

Allergic reactions in PLWHIV tend to have a delayed onset, with severe hypersensitivity reactions such as SJS and TEN occurring more frequently. Studies by Evi and Coopman et al suggest two mechanisms of drug reactions: the hapten pathway and direct T-cell activation via the major histocompatibility complex (MHC). CD4+ T cells release cytokines such as interleukin-5 (IL-5), granzyme, and eotaxin, which play a role in eosinophil differentiation.[8] ART can trigger cutaneous adverse drug reactions (CADR), ranging from mild rashes to severe allergic reactions. A study by Coopman et al found that CADR occurred in 8.2% of PLWHIV, with morbilliform rashes being the most common, often caused by cotrimoxazole and ART.[7,9] This literature review summarizes the impact of immune dysregulation in PLWHIV on increased allergy risk, despite ART effectively controlling viral load. Residual immune dysregulation may elevate the risk of allergic conditions such as asthma and dermatitis. This review also identifies knowledge gaps, provides guidance for healthcare professionals, and highlights research opportunities to improve treatment and quality of life for PLWHIV.

LITERATURE REVIEW

The research design used in this study is a literature review method, utilizing the keywords 'immune dysregulation,' 'HIV infection,' 'hypersensitivity,' and 'antiretroviral' to identify studies related to residual immune dysregulation syndrome. The literature sources include PubMed, Google Scholar, ScienceDirect, EBSCO, and Hindawi. The authors then reviewed each journal that met the criteria, engaged in discussions, and conducted cross-checks with other primary sources.

RESIDUAL IMMUNE DYSREGULATION PHENOMENOM IN HIV

Research on simian immunodeficiency virus (SIV) infection in non-human primates (NHP) reveals that although the infection causes CD4 decline and viremia in both host types, it only leads to more severe disease in Asian NHPs. This occurs due to persistent activation of the innate and adaptive immune systems in non-natural hosts, in contrast to temporary inflammation in natural hosts. Similarly, HIV in humans causes chronic inflammation, which plays a role in coagulopathy and contributes to poor health outcomes.[10] Biomarkers such as D-dimer, IL-6, and soluble CD14 (sCD14) are associated with increased mortality in PLWHIV, and immune activation is often a better predictor of poor outcomes than viral load.[11,12]

Although ART reduces inflammatory biomarkers, some remain elevated in PLWHIV, even when treatment is initiated during acute HIV infection. Studies on elite controllers (EC) show that despite maintaining low viral loads, chronic immune activation persists and can lead to a decline in CD4+ T cell counts and AIDS progression. Chronic immune activation also occurs in EC, as evidenced by a reduced percentage of naive cells, increased monocyte activation markers, and soluble inflammatory mediators. This indicates that persistent immune dysfunction plays a role in the pathogenesis of RIDS, despite controlled viral load.[10,13,14]

In HIV patients undergoing ART, although CD4 counts generally increase, about 60% fail to achieve normal CD4 levels (>500 cells/μL) after 4 years, and 6% do not even reach >200 cells/μL. Factors such as irregular ART use or initiating treatment at an advanced stage of infection can influence immunological recovery. ART can increase CD4+ T cell counts in peripheral blood, but recovery in lymphoid tissues, particularly in the gut, is often incomplete.[15] Moreover, ART does not always restore the balance of naive, effector, and memory T cells and can lead to functional defects in CD4+ and CD8+ T cells. Innate immune system disturbances, such as monocyte activation and alterations in NK cells, neutrophils, and dendritic cells, persist despite viral load suppression. Some innate immune cells, such as IL-17- and IL-22-producing lymphoid cells, as well as MAIT (Mucosal-associated invariant T) cells, also do not fully recover, contributing to gut barrier dysfunction and increased susceptibility to infections. Additionally, defects in humoral immunity, such as a decline in protective antibodies, further increase vulnerability to certain diseases despite ART treatment.[16,17]

RESIDUAL IMMUNE DYSREGULATION PHENOMENOM IN ALLERGY

CD4+ T cells proliferate and differentiate into several subsets, including Th1 and Th2, functioning as key regulators of the immune system. Interferon gamma (INF-γ) and interleukin 2 (IL-2) are crucial mediators of the cellular immune response produced by Th1.[18-20] Mu et al stated that one of the consequences of chronic inflammation from HIV infection is T cell exhaustion, where these crucial immune cells become less effective, with a reduced capacity to efficiently eliminate infected cells. Metabolic imbalance leads to T cell metabolic stress, immune activation, and T cell dysfunction (Figure 1). Despite undergoing ART, HIV infection causes persistent immune activation and metabolic alterations in T cells, characterized by increased type 1 INF-γ, elevated reactive oxygen species (ROS), mitochondrial dysfunction, etc. Persistent immune activation and metabolic stress ultimately.[5,21,22]

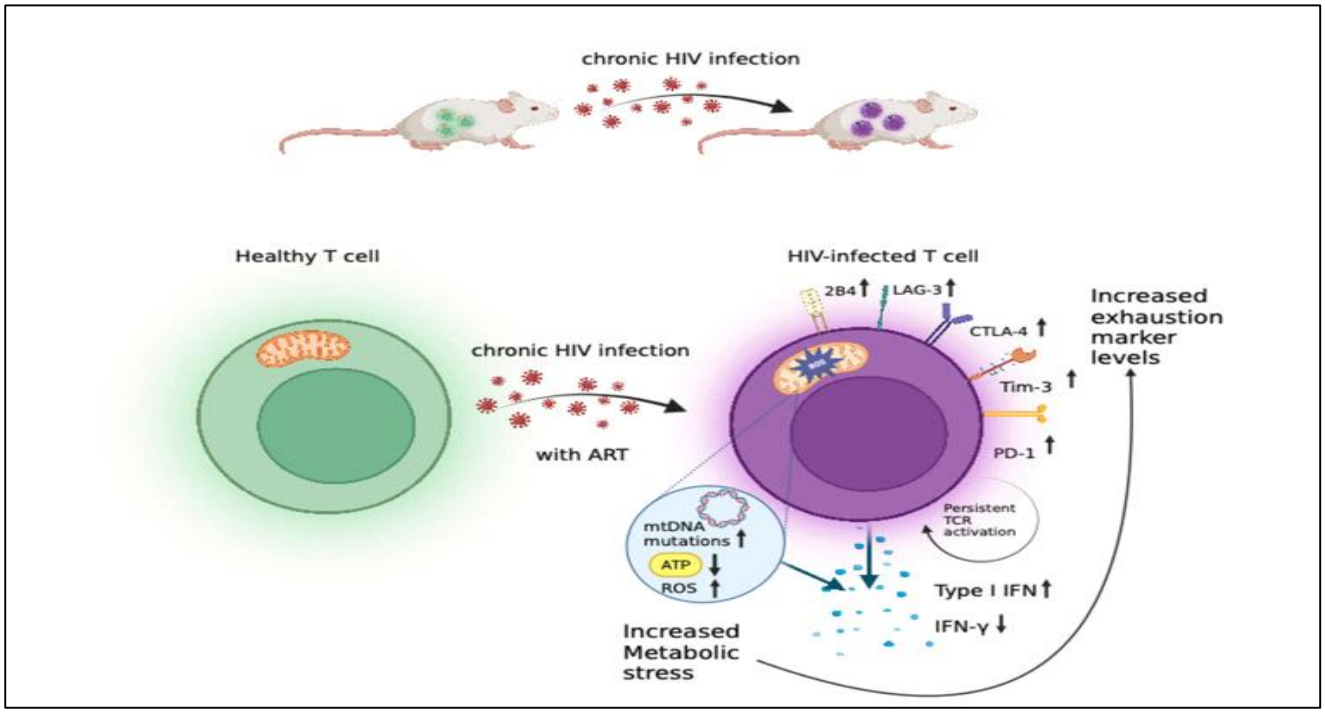

Figure 1: Metabolic process imbalance, whether directly caused by HIV infection or indirectly triggered by the inflammatory response induced by HIV in immune cells, contributes to immune activation and dysfunction.[22]

In the late stage of HIV infection, Th1 cell cytokine production declines, while Th2 cells produce IL-4, IL-5, IL-6, and IL-10, which serve as mediators of the humoral immune response and aid B lymphocytes in antibody production. Clinical findings support that IL-4-driven B cell activity promotes IgE production, with significantly increased serum IgE levels being associated with a decrease in CD4+ cell count to <200/mm^2. HIV-infected cells are susceptible to drug metabolite-induced damage, triggering cytokine release and hypersensitivity, while low glutathione levels and Tat expression exacerbate oxidative stress and viral replication.[23]

DISCUSSION

HIV infection and hypersensitivity events

PLWHIV are known to have a higher risk of allergic reactions compared to the non-HIV population. This is thought to be related to persistent immune system dysregulation, even after receiving ART. Various forms of allergies, such as drug hypersensitivity, AD, allergic rhinitis, and asthma, are more frequently reported in PLWHIV. A study by Becker et al found that allergic manifestations, such as asthma, were 15.5% more prevalent in PLWHIV compared to non-PLWHIV. HIV-1 infection triggers a shift in immune response from Th1 to Th2, increasing IgE synthesis and Th2 cytokines, similar to an allergic response. IL-4 plays a role in inducing CXCR4, which facilitates the replication of viral variants. A recent hypothesis suggests that viral proteins may contain allergen-like domains that trigger Th2 activation. Potential therapeutic approaches include genetic engineering to remove these domains in vaccine development and IL-4 inhibition to restore the Th1/Th2 balance.[19]

A retrospective study at Dr. Soetomo general hospital, Surabaya (2013-2015), found that 62.5% of cases of cutaneous adverse drug reactions (CADR) in PLWHIV were related to ART, primarily in males (65%) aged 25-44 years (85%). Maculopapular rash was the most common manifestation (65%), followed by SJS (20%), erythroderma (5%), and TEN (5%). Nevirapine (NVP), a first-line NNRTI antiretroviral, was the most frequently associated with CADR in outpatient HIV patients, with an incidence of maculopapular rash (56.12%) and pruritus/urticaria (62.5%). Besides nevirapine, efavirenz, zidovudine, lamivudine, and atazanavir were also frequently associated with maculopapular rash.[24] Abacavir (ABC) has the potential to cause allergic reactions that require special attention. Multivariate analysis found that higher CD8+ T cell proliferation (>850 vs. ≤850 cells/mm^3) has been demonstrated using carboxyfluorescein diacetate succinimidyl ester in peripheral blood of patients with a positive patch test for abacavir. Genetic susceptibility to abacavir allergy is also evident through the HLA allele HLA-B*5701, with a positive predictive value of more than 70% and a negative predictive value of 95-98%.[30]

A case-control and retrospective group study by Guevara et al examined 142 and 193 PLWHIV, comparing the number of positive tests and papule size ($p<0.001$ in both cases). Among the 193 PLWHIV included, respiratory allergic manifestation (RAM) was found in 11.01%, with

the risk of developing RAM being 2.5 times higher in patients with CD4+ >200/mm^3.[25] The results of this study contrast with those of Israel-Beith et al who demonstrated the strongest association between IgE concentration and CD4+ count <300/mm^3, with an AIDS incidence rate of 83% in individuals with elevated IgE compared to 44% of individuals (n=28) with normal serum IgE levels. Analysis of patients with elevated IgE levels using radioallergosorbent test (RAST) showed a rate of 36-44% in advanced-stage HIV compared to 7% in non-PLWHIV (seronegative) controls. Their study also found a correlation between advanced-stage HIV infection, secondary infections, and increased IgE levels, further exploring the biological relevance of cytokine-mediated responses.[26] Clerici et al conducted an in vitro study on HIV-induced programmed T-cell death. Their research found that exogenously added IL-2 and IFN-γ (Th1 cytokines) blocked activation-induced programmed cell death, whereas Th2 cytokines (IL-4, IL-5, IL-6, and IL-10) enhanced apoptosis. This effect provides a mechanism for the immunopathogenesis of T-cell depletion and HIV disease progression.[27]

Clinical implications and treatment of allergies in PLWHIV

The management of allergies in PLWHIV faces unique challenges due to the phenomenon of persistent residual immune system dysregulation, even after receiving ART. The unstable immune mechanisms in these patients can lead to more severe or atypical allergic responses, making diagnosis and treatment more challenging. Additionally, the high incidence of drug hypersensitivity, limited treatment options, and comorbidities such as OIs further complicate allergy management in this population. AD is a chronic inflammatory skin disorder often associated with other atopic conditions such as asthma and allergic rhinitis. In a case series of four PLWHIV patients reported by Alwadhi et al prior to 2017, the primary treatment for AD focused on topical therapy. Since 2017, dupilumab, a monoclonal antibody targeting the interleukin-4 receptor alpha (IL-4Rα), has become the first-line treatment for moderate to severe AD due to its high efficacy and favorable safety profile.[28] A case report by Brodska et al. demonstrated an improvement in PLWHIV with AD and asthma who had failed previous therapy after receiving dupilumab.[29]

Additionally, drug allergies are 100 times more common in PLWHIV, and AIDS increases the risk of SJS and TEN by 1,000 times compared to the non-PLWHIV population. Drug reactions, particularly to trimethoprim-sulfamethoxazole (TMP/SMX), occur more frequently in PLWHIV, rising from 2-8% in the general population to 43% in HIV and 69% in AIDS. Risk factors include polypharmacy, slow acetylator status, glutathione deficiency, CD4 <200 cells/mm^3, latent CMV and EBV infections, and CD8 >460 cells/mm^3. Approximately 50-60% of patients using TMP/SMX develop a rash and fever within 1-2 weeks of therapy. Mild symptoms can be managed with antihistamines and topical corticosteroids, while persistent cases require dose reduction or oral corticosteroids at 0.5 mg/kg for 21 days. Desensitization is successful in 63% of cases but must be conducted in a tertiary care facility. The main challenges in therapy include the risk of severe reactions and the need for close monitoring.[30]

Drug classes such as NRTIs (Abacavir) and NNRTIs (Nevirapine) are also known to cause allergic reactions in PLWHIV and require special attention. NVP can be administered at a lower dose during the first two weeks, followed by 200 mg twice daily. If a rash appears within the first two weeks of observation, the medication should be postponed until the rash resolves.[31,32] Genetic screening for HLA-B5701 is effective in reducing the incidence of ABC hypersensitivity from 8% to 2%. However, the possibility of allergic reactions may still occur due to negligence in reviewing the screening results before prescribing the medication.[31] Numerous studies have discussed the mechanisms of allergy and hypersensitivity in PLWHIV. However, there are currently no specific guidelines in Indonesia regarding allergy management in this population. The high incidence of drug hypersensitivity, limited availability of safe therapies, and the risk of severe reactions such as SJS and TEN highlight the need for a more systematic approach to diagnosis and management. Genetic screening, such as HLA-B5701, has been proven to reduce the risk of hypersensitivity to Abacavir, but challenges remain in its implementation. Therefore, further research is needed to develop national guidelines that can assist clinicians in optimally managing allergies in PLWHIV in the ART era.

CONCLUSION

Although ART effectively suppresses HIV viral replication, residual immune dysregulation remains a significant concern in PLWHIV, contributing to chronic immune activation, systemic inflammation, and an increased risk of allergic conditions. The shift from a Th1 to a Th2-dominant immune response leads to heightened IL-4, IL-5, and IL-13 production, promoting IgE-mediated hypersensitivity reactions. Drug hypersensitivity, particularly to Nevirapine and Abacavir, poses severe risks, including SJS and TEN. The absence of specific clinical guidelines in Indonesia for allergy management in PLWHIV highlights the need for further research to develop tailored approaches that improve diagnosis, treatment, and overall patient care. Addressing immune dysregulation in PLWHIV is essential for enhancing their quality of life and mitigating severe allergic complications associated with HIV infection and its treatment.

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