

HIV AND ALLERGY

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The past two decades have seen the emergence of two apparently unrelated pandemics – HIV/AIDS and allergic disorders. The relatively rapid rise in allergic disorders points to important environmental determinants associated with socio-economic development, which may interact with an underlying genetic predisposition to atopy. The rapid spread of the HIV/AIDS pandemic can be attributed to various viral and socio-economic factors.

Other than possible underlying socio-economic factors, there is no apparent association between these two disorders. AIDS is an acquired immunodeficiency of viral aetiology, whereas atopic disorders result from the overproduction of immunoglobulin E (IgE) in response to allergens. Recent research¹ has, however, shed a new light on the relationship between these two disorders. Evidence of increased IgE levels has been found in HIV-infected individuals. This increased IgE is associated with a shift from a T helper-1 (Th1) to a T helper-2 (Th2) cytokine profile and histamine release from mast cells and basophils in response to HIV viral antigens. There is also *in vitro* evidence that the HIV virus can infect mast cells and basophils.¹

CLINICAL MANIFESTATIONS OF ATOPY IN HIV-INFECTED INDIVIDUALS

Hypersensitivity and allergy are significant problems in many HIV-infected individuals, commonly occurring before immunodeficiency is clinically evident. Not only is the prevalence of atopy increased in these patients, but also the severity of their allergic reactions.

The most common manifestation of allergy in HIV-infected individuals is drug allergy, particularly to sulphonamide-containing drugs such as trimethoprim-sulfamethoxazole (TMP-SMX) and dapsone, but reactions occur to other drugs including rifampicins and antiretrovirals. Most often this involves non-nucleoside reverse transcriptase inhibitors (NNRTIs), but allergy is also well described with zidovudine, abacavir and amprenavir. Clinically, most patients present with an erythematous rash, which in approximately 0.5% of cases is blistering in nature.² The rash may be accompanied by fever, and in some cases by systemic reactions.

Other forms of atopy are also common in these individuals, the most notable of these being allergic rhinitis and atopic skin disorders.^{3,4} Usually allergic manifestations subside late in the disease when energy develops and delayed-type hypersensitivity reactions are diminished. However, patients with advanced HIV disease and a history of allergic contact dermatitis may continue to show positive reactions to certain allergens.⁵

PATHOGENESIS OF HIV-ASSOCIATED ATOPY

Evidence from recent research¹ has elucidated interactions between the HIV virus and the immune system that may lead to the development of allergic manifestations.

HIV-1 ENVELOPE PROTEIN GP120 INDUCES INTERLEUKIN (IL)-4 AND IL-13 RELEASE FROM MAST CELLS AND BASOPHILS

HIV enters the body predominantly through mucosal surfaces, where mast cells are particularly abundant. The HIV virus surface protein, gp120, is a member of the immunoglobulin (Ig) superantigen family. Ig heavy chain variable 3 (VH3) gene products are the ligands for gp120. Gp120 interacts with the VH3 region of IgE on the surface of mast cells and basophils and thereby activates these cells to secrete IL-4, IL-13, histamine and other allergic mediators.¹

HIV-1 TRANSACTIVATOR PROTEIN (TAT) IS CHEMOTACTIC TO AND ACTIVATES HUMAN MAST CELLS AND BASOPHILS

The HIV-1 Tat protein is a promiscuous transactivator of viral and cellular genes. This transactivation leads to three important events involved in the interaction between HIV and cellular determinants of allergy: (i) Tat induces secretion of IL-4 and IL-13 from mast cells and basophils; (ii) Tat protein causes chemotaxis of mast cells and basophils that contributes to the recruitment of these cells to the site of HIV infection; and (iii) Tat upregulates β -chemokine receptor 3 (CCR3), a co-receptor for macrophage (M)-tropic strains of HIV, on the surface of mast cells and basophils.¹

INCREASED LEVELS OF IL-4 AND IL-13 LEAD TO A TH2 SHIFT AND INCREASED LEVELS OF IGE IN HIV-INFECTED PATIENTS

IL-4 and IL-13 are produced by Th2 cells, mast cells and basophils. IL-4 and IL-13 stimulate the differentiation of Th0 cells into Th2 cells, thereby causing a shift from a Th1 cytokine profile to a Th2 cytokine profile (IL-4 and IL-13). IL-4 and IL-13 also stimulate B-cells to switch to IgE production.⁶ IgE bound to mast cells and basophils can then be bound by normal allergens or gp120 as superantigen. This cycle contributes directly as well as indirectly to immune deregulation caused by HIV infection and is involved in the pathogenesis of allergic manifestations in these patients.¹ The role of HIV in the pathogenesis of allergic reactions is illustrated in Fig. 1.

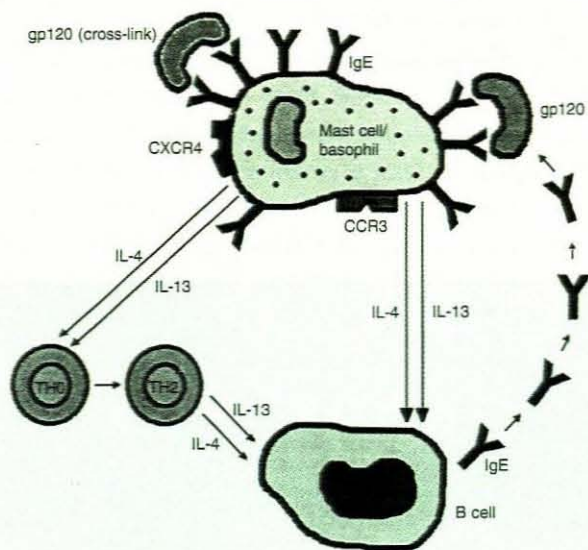


Fig. 1. Pathogenesis of allergic reactions in HIV infection.

HIV CAN ACTIVELY INFECT MAST CELLS AND BASOPHILS

Mast cells and basophils express CD4, the receptor for HIV, on their surfaces. The two main co-receptors for the HIV virus, CCR3 and α -chemokine receptor 4 (CXCR4), are constitutively expressed on the surfaces of mast cells and basophils, while the expression of CCR3 is upregulated by Tat protein. Furthermore, mast cells and basophils have been successfully infected by M-tropic strains of HIV-1 *in vitro*. This leads to the hypothesis that infected basophils/mast cells can carry HIV to lymph node lymphocytes and across the blood-brain barrier to microglia and astrocytes. Interestingly, mast cell density is increased in lymph nodes from AIDS patients, and mast cells are one of the few types of immune cells found in the brain.¹

MANAGEMENT OF ALLERGIES IN HIV-INFECTED PATIENTS

Atopy is an ever-increasing problem in HIV-infected individuals and is becoming even more prominent in the highly active antiretroviral treatment (HAART) era. Not only are the patients developing hypersensitivity to the drugs used for HAART, but immune reconstitution prevents the loss of delayed-type hypersensitivity due to anergy that characterises progression of HIV infection.

DRUG ALLERGY

Drug sensitivity is the most important allergic condition, with far-reaching implications. In managing an HIV-infected individual with a drug allergy, the allergy-inducing drug should be substituted for an acceptable equivalent where available. Unfortunately this is not always possible. Further management will depend on the type of drug and indication for use. The most common drug allergy encountered in HIV-infected patients is to TMP-SMX. If the reaction is not severe, a single-strength tablet can be substituted for a double-strength tablet or the dosage changed to one tablet 3 days per week. If reactions persist, desensitisation can be considered.⁷ A simple regimen with a starting dose of 0.4 mg TMP/2 mg SMX, with incremental increases in the daily dose to reach a dose of 80 mg TMP/400 mg SMX by day 5 carries a success rate of approximately 95%.² Desensitisation protocols have been published for many other drugs used in HIV-infected individuals, such as rifampicin, isoniazid, ethambutol and zidovudine.⁸

Abacavir, a nucleoside reverse transcriptase inhibitor, has been associated with life-threatening hypersensitivity in 3 - 5% of patients. In cases of proven or suspected hypersensitivity, abacavir should be discontinued, and rechallenge (which can be rapidly fatal) should not be attempted.²

The NNRTIs delavirdine, efavirenz and nevirapine have all been associated with allergic manifestations. These reactions are more frequent with nevirapine and delavirdine, but the reactions associated with nevirapine are more severe. The issue of cross-sensitivity between the NNRTIs has not been resolved, but is estimated to be about 70%.² It is therefore not recommended that another NNRTI be used in patients with a previous severe reaction to a drug in this group.

OTHER ATOPIC DISEASES

The therapeutic approach to allergic conditions is similar to that for any other atopic patient. Antihistamines can be

used safely and effectively in HIV-infected patients. Corticosteroids should, however, be used with caution. The use of allergen immunotherapy (AIT) for allergic respiratory disease in HIV-infected patients is undergoing investigation.⁹ Data from pilot studies and case reports suggest that AIT may be safe and effective in HIV-infected patients, at least in those with early or moderate disease. Despite the lack of data and given the theoretical grounds for believing that AIT may be safe and effective it seems reasonable to proceed, with appropriate informed consent. However, in the light of the increased reaction to drugs seen in many persons with HIV, careful test dosing may be necessary.

CONCLUSION

As the HIV pandemic progresses in South Africa an increasing number of HIV-infected patients will present with atopic disorders. Clinicians treating these patients will have to integrate available knowledge into an effective

management plan for these patients. In this exciting time of ever-expanding knowledge of HIV and allergy a rapid expansion of knowledge, approaches, and treatment modalities ultimately benefiting the atopic HIV-infected patient can be expected.

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