

# HUMAN IMMUNODEFICIENCY VIRUS AND ALLERGIC DISEASE

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## ABSTRACT

The relationship between human immunodeficiency virus (HIV) infection and allergy is not clearly understood, but there does not appear to be a direct association between them. IgE levels are increased in HIV-infected persons, but this appears to be due to a loss of appropriate host immune response rather than associated with atopy. Asthma is common in HIV-infected patients and must be differentiated from other causes of wheezing. Chronic nasal symptoms and sinusitis are common in HIV infection, and may be associated with allergy. Opportunistic infections can present as or complicate allergic disease. Management of allergic conditions in HIV-infected patients follows the same principles as in HIV-uninfected persons, but the treating doctor must be aware of possible drug interactions between antiretroviral therapy and allergy treatment. Drug hypersensitivity (DH) reactions are more common in HIV-infected patients, and may be related to antiretroviral drugs or to drugs used to treat concomitant infections. DH typically presents with an erythematous maculopapular rash with constitutional symptoms. Desensitisation may be successful, particularly for cotrimoxazole, but is contraindicated in abacavir as re-exposure to this drug results in severe hypersensitivity reactions.

## INTRODUCTION

The human immunodeficiency virus (HIV) was discovered to be the cause of the acquired immunodeficiency syndrome (AIDS) in the USA in the early 1980s. Since then it has infected more than 40 million people worldwide, and is particularly prevalent in sub-Saharan Africa, notably in South Africa.<sup>1</sup> The introduction of highly active antiretroviral therapy (HAART) has led to a dramatic decline in the morbidity and mortality of this disease worldwide. Health care professionals caring for HIV-infected people have described that their patients frequently present with symptoms that are identical to those of allergic disease, such as skin rashes, wheezing, drug hypersensitivity, and rhinitis and sinusitis.<sup>2</sup> The relationship between the manifestations of hypersensitivity and the immunological changes secondary to HIV infection is still not clearly understood.

In this article, we present an overview of the association between allergy and HIV disease, together with management of the various conditions, and then discuss drug hypersensitivity (DH) reactions and their management.

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## ATOPY, ALLERGY AND HIV DISEASE – IS THERE A LINK?

Atopy and allergic conditions are common in the general population. With the increasing prevalence of HIV disease and AIDS, it follows that these conditions will also affect this population group.

Both HIV and allergic disease stem from immune-mediated reactions. However, the difficulty comes in ascertaining if there is a causal link (association) between the two. The literature does not suggest a direct association between atopic disease and HIV.

### *Immunology of an allergic reaction*

An allergic reaction is a type 1 mediated hypersensitivity response caused by re-exposure to a specific antigen (allergen). Atopy is typically a T helper cell 2 (Th2) immunological response.

The immunology of an allergic reaction involves primary exposure to an allergen, during which a naive B lymphocyte undergoes class differentiation into an IgE antibody-secreting cell. These IgE antibodies then bind to tissue mast cells and blood basophils causing 'sensitisation' of these cells. Later exposure to the same allergen causes degranulation of mast and basophil cells with release of histamine, leukotrienes and prostaglandins.<sup>3</sup>

### *Immunology of HIV disease*

Damage to the immune system by the HIV occurs via three mechanisms:

- harm to the infected host cells
- harm to non-infected cells by virions and virion particles and
- chronic cell activation.

The immune system is highly interlinked and this results in dysfunction to other cell types.<sup>4</sup>

The primary cell type involved in HIV infection is the CD4 cell. The target cells are usually susceptible macrophages and CD4 helper T lymphocytes. HIV binds to a primary (CD4) receptor and then a co-receptor (CCR5 or CXCR4) on the target cell. This then allows fusion of the virus into the cell. After migration to the nucleus reverse transcription of the RNA occurs with the formation of viral DNA which is incorporated into host viral DNA. This then leads to the transcription of viral RNA and the synthesis of new HIV virions.<sup>2,3</sup>

Studies have demonstrated an increase in IgE levels in HIV-infected people (both adults and children).<sup>2,5</sup> It has also been found that IgE levels increase with disease progression and decrease in CD4 counts. However, these increases in IgE levels are not directly associated with atopy or allergic disease but may signal a loss of appropriate host immune response.

### *Asthma*

Asthma is common in patients with HIV infection, however the prevalence is not known.

Patients with HIV may wheeze for many reasons and the challenge lies in differentiating allergic asthma from other causes of wheezing.<sup>6</sup> Some causes of wheezing other than asthma in HIV-infected patients are listed in Table I.

**Table 1. Differential diagnosis of asthma in HIV-infected patients**

<b>Large airway obstruction</b>
Tuberculous lymph node enlargement
Lymphoma
Kaposi's sarcoma
Immune reconstitution inflammatory syndrome (IRIS)
Foreign body
<b>Lower airway obstruction</b>
Gastro-oesophageal reflux with/without aspiration
Swallowing incoordination with aspiration
Lymphocytic interstitial pneumonitis (LIP)
<b>Other</b>
Cardiomyopathy

Diagnosing asthma in HIV-infected people should be based on the same methods as those used in the HIV-uninfected population. A history of atopy, allergic triggers and coexisting conditions such as allergic rhinitis and eczema are suggestive of a diagnosis of asthma as opposed to other causes of wheezing. Pulmonary function tests can confirm the presence of airway obstruction in patients with asthma. Increased incidence of airway hyperresponsiveness has not been reported in HIV-infected patients without asthma.<sup>6</sup>

Treatment of asthma in HIV-infected patients must take into account drug interactions that may occur. Certain antiretroviral drugs (e.g. the protease inhibitor ritonavir) induce the cytochrome P450 metabolism system and the concurrent use of HAART and other medications used in the treatment of asthma and allergy (e.g. antihistamines) may cause interactions of clinical significance.<sup>6</sup> In general the treatment for HIV-infected patients with asthma follows the same guidelines as those used for the general population. This includes controller therapy with inhaled corticosteroids (ICS) and the use of a bronchodilator for acute relief of airway obstruction. Systemic corticosteroids may be used for acute exacerbations and it has been shown that both short- and long-term corticosteroid use is no more deleterious in HIV-infected individuals than in the general population.<sup>6</sup> Oral candidiasis, a side-effect of ICS, may be more frequently observed in HIV-infected patients.

It is important to rule out concurrent acute or chronic pulmonary infection in HIV-infected asthmatic patients who present with wheezing.

A recent large study concluded that HIV-infected children commenced on HAART were three times more likely to develop asthma than HIV-positive children not on HAART.<sup>7</sup> It is postulated that improved cellular immunity and higher CD4 counts may lead to airway hypersensitivity and the development of asthma. Health care professionals need to be aware that asthma may develop in children with immune reconstitution and thus manage these children appropriately.

### **Allergic rhinitis/rhinoconjunctivitis and sinusitis**

Rhinitis, characterised by symptoms of sneezing, nasal blockage, rhinorrhoea and itching, is the result of both humoral and cellular immune reactions to airborne allergens. There is a release of inflammatory mediators from IgE-dependent mast cells in the nasal mucosa.<sup>8</sup>

Rhinitis may be of allergic (IgE-mediated) or non-allergic (non-IgE-mediated) type. In HIV-infected patients, chronic nasal symptoms are common and the chal-

lenge lies in differentiating true allergic rhinitis from other chronic nasal conditions.<sup>2,9</sup> Other causes of upper airway obstruction in HIV-infected individuals include lymphoid hyperplasia, adenotonsillar hypertrophy and Kaposi's sarcoma.

Clinical evaluation of rhinitis includes a thorough history, looking for an association with allergen exposure, a physical examination in which pale blue-tinged nasal turbinates with thin, clear nasal secretions are seen, and a nasal smear which may be normal or show eosinophil predominance.<sup>9</sup> Associated clinical features may include infraorbital 'shiners', scleral or conjunctival inflammation, otitis media, sinusitis or nasal polyps.

Skin-prick testing with appropriate allergens is the most sensitive and useful way to confirm allergy. It is more cost-effective than allergen specific IgE.<sup>10</sup>

Treatment of allergic rhinitis follows the same principles as those for HIV-uninfected people. Allergen avoidance is useful in combination with pharmacotherapy which includes intranasal corticosteroids and oral antihistamines. Once again it is important to consider drug interactions that may occur in people on HAART.<sup>2,9</sup>

Allergic conjunctivitis tends to coexist with allergic rhinitis, asthma and urticaria. There is no association between rhinoconjunctivitis symptoms and CD4 cell depletion.<sup>11</sup>

Sinusitis is a common comorbidity of rhinitis. Several studies have reported sinusitis associated with allergy in HIV-infected patients, with incidences ranging from 10% to 68%.<sup>12-14</sup> Allergic nasal inflammation and blockage of the sinuses can lead to secondary bacterial infection. The most common organisms implicated in secondary bacterial infection include *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, but there may also be infection with atypical organisms including fungi.<sup>14</sup>

Treatment of sinusitis involves reducing allergic inflammation with intranasal corticosteroids, as well as treatment of infection with antibiotics. Owing to the risk of severe secondary infection, chronic nasal symptoms in the HIV-infected patient warrant early and aggressive treatment.

### **Atopic eczema**

Atopic eczema characteristically manifests with erythematous scaling plaques with associated pruritus. There may also be secondary lichenification with excoriations and secondary bacterial infection.<sup>15</sup> Atopic dermatitis is common in HIV-infected patients and is often resistant to treatment. A possible explanation for this is the similar cytokine profile in both HIV and atopic dermatitis. Both demonstrate a Th2 cytokine profile with elevated IgE levels, increased eosinophils and increased interleukin 4 and 5.<sup>15</sup>

A history, careful physical examination and histopathological findings are all used in the diagnosis of atopic eczema. A history of atopy is useful in making the diagnosis, but its absence does not exclude the diagnosis. The differential diagnosis of atopic dermatitis would include psoriasis, cutaneous T-cell lymphoma and drug eruptions. Histologically there is epidermal hyperplasia with perivascular infiltrates of eosinophils and lymphocytes. Although non-specific, atopic dermatitis may be associated with elevated IgE levels and peripheral eosinophilia.

Treatment includes avoidance of irritants, the use of emollients, topical corticosteroids and oral antihistamines. Antiretroviral therapy is important in the management of atopic dermatitis and reduces the severity of the condition. Topical calcineurin inhibitors (pime-

crolimus cream 1% and tacrolimus ointment 0.03% and 0.01%) have been shown to be safe alternatives to topical steroid treatment and exhibit a more selective mechanism of action. They are also not associated with other systemic immunosuppression and are safe to use in HIV-infected patients.<sup>16</sup>

### **Allergen immunotherapy (AIT) in HIV-infected patients**

The use of allergen immunotherapy (AIT) in HIV-positive patients is controversial in that there is a concern over decreased efficacy and causing progression of the underlying HIV disease. Theoretically AIT should be a safe and efficacious method of controlling atopy in HIV-positive patients.<sup>17</sup>

The relationship between HIV and atopic disease needs further investigation and follow-up, particularly in children. A recent study showed no increased prevalence of atopy in perinatally infected HIV-positive patients.<sup>18</sup> Further longitudinal studies may help in establishing other correlations between the two conditions.

### **HIV AND DRUG HYPERSENSITIVITY (DH)**

Adverse drug reactions have been described in 10-20% of patients in hospital, and affect approximately 7% of the general population.<sup>19</sup> The use of HAART together with therapy for HIV-associated infections has resulted in new concerns regarding DH and other drug reactions.

### **Pathophysiology of DH in HIV**

In 1972 the World Health Organisation defined an adverse drug reaction as a 'response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function'.<sup>20</sup> This definition is considered too broad and too vague, and an alternative definition was proposed by Edwards and Aronson: 'An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product'.<sup>21</sup>

DH occurs in a relatively small number of patients but these reactions are often associated with significant morbidity and mortality. The pathogenesis of DH reactions is not well defined, but many of the drugs implicated in causing DH are metabolised to reactive oxidative intermediates. It is thought that these reactive drug products are at least partially responsible for DH, as explicated by two theories.<sup>22</sup> The first theory is known as the 'hapten hypothesis' where the reactive drug products covalently bind to tissue macromolecules to produce antigens, which then initiate a host response. According to the other theory, the 'danger hypothesis', oxidative cell damage from reactive drug metabolites causes cytokine release, which in turn results in an immune response to eradicate these modified 'dangerous' cells.<sup>22,23</sup>

DH reactions have been described to be 100 times more common in HIV-infected patients, but are clinically similar to those presenting in HIV-uninfected patients. The usual presentation is with fever, skin rash and internal organ involvement, usually within 4-6 weeks of initiating drug use, but it may also occur within the first week.<sup>23,24</sup> The increased occurrence of DH or drug eruptions in individuals living with HIV has been attributed to the dysregulation of the immune system which makes them vulnerable to oxidative stress. The

factors that make the individual HIV-infected patient more susceptible are unknown, but a combination of factors such as immunological status, recurrent or concurrent infections, genetics and medication use are probably involved.

### **Clinical presentation and diagnosis**

The typical presentation of a DH reaction is an erythematous maculopapular or morbilliform rash together with constitutional symptoms such as fever, myalgia and rigors. The constitutional symptoms may precede the rash. The hypersensitivity reaction can vary from a rash with or without angio-oedema to severe anaphylactic shock.

Typically the rash is pruritic and confluent in nature and is most prominent on the body and arms. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare and occur in about 0.5% of patients.<sup>25</sup> If an individual has been previously exposed to the drug or has had a hypersensitivity reaction to the drug the reaction may develop within a few hours.

The term 'drug hypersensitivity syndrome' (DHS) describes a severe reaction to drugs which includes the following: skin rash, constitutional symptoms and internal organ involvement.<sup>23</sup> The constitutional symptoms and signs described are fever, lymphadenopathy and pharyngitis. The organ systems that are particularly involved are the liver (hepatitis), kidneys (nephritis) and the haematopoietic system (neutrophilia, eosinophilia, atypical lymphocytosis, blood dyscrasias and haemolytic anaemia).<sup>23</sup>

The diagnosis of a hypersensitivity reaction is based on the specific history and clinical manifestation. The most important information required for the clinical diagnosis is the time of onset of symptoms after the initiation of therapy.<sup>26</sup> In HIV-infected individuals it is further essential to have knowledge about HAART and drugs used to treat HIV-associated infections and their different drug reactions and interactions. Unfortunately there is no specific or optimal laboratory test that can be used to confirm the diagnosis of a hypersensitivity reaction. Intradermal skin testing and patch testing have been used to identify the causative drugs, but their accuracy is uncertain.<sup>26</sup>

Table II lists information for assessing suspected drug allergy.

**Table II. Important information in assessing suspected drug allergy\***

Description of the reaction: symptoms, duration
Timing of symptoms in relation to administration of drug
Duration of treatment with suspected drug
Underlying illnesses
Concomitant drugs (including over the counter treatments)
Past medical and drug history

\* Adapted from Mirakian *et al.*<sup>32</sup>

### **Antiretroviral therapy associated hypersensitivity reactions**

Antiretroviral therapy has been categorised in the following groups: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and the newer group, the fusion inhibitors (FIs). The categories of antiretroviral therapy together with examples are listed in Table III.<sup>27</sup>

**Table III. Commonly used antiretroviral drugs by class of action**

NRTI/NtRTI	NNRTI	Protease inhibitor	Fusion inhibitor
Zidovudine (ZDV)	Nevirapine (NVP)	Indinavir (IDV)	Enfuvirtide (T-20)
Didanosine (ddI)	Efavirenz (EFV)	Ritonavir (RTV)	
Stavudine (d4T)		Nelfinavir (NFV)	
Lamivudine (3TC)		Lopinavir/r (LPV/r)	
Tenofovir (TDF)		Fosamprenavir	
Combivir (COM)			
Abacavir (ABC)			

NRTI – nucleoside reverse transcriptase inhibitor; NtRTI – nucleotide reverse transcriptase inhibitor; NNRTI – non-nucleoside reverse transcriptase inhibitor.

### Nucleoside reverse transcriptase inhibitors (NRTIs)

The drug responsible for the most hypersensitivity reactions in this class is abacavir. The hypersensitivity reaction associated with abacavir is characterised by fever, skin rash and a combination of other symptoms such as headache, gastrointestinal and other constitutional symptoms. It occurs within 6 weeks of initiating therapy.<sup>24,27</sup>

Laboratory abnormalities that have been recorded are elevated transaminases and creatinine phosphokinase. There has been an association between abacavir hypersensitivity and the major histocompatibility complex (MHC) class I allele HLA-B\*5701, HLA-DR7 and HLA-DQ3.<sup>24,27</sup> Abacavir patch testing has been used to identify the immunogenetically mediated abacavir hypersensitivity reaction. The abacavir patch test has a shorter turnaround time and is more cost-effective than the usual molecular typing methods.<sup>24</sup> Most of the genetic methods are still being investigated.

Desensitisation is contraindicated in abacavir because re-exposure to this drug after a hypersensitivity reaction has resulted in an increase in severity and rapidity of hypersensitivity symptoms.

The other NRTIs are not associated with hypersensitivity reactions but minor skin rashes may develop. There is no known cross-reactive hypersensitivity between the NRTIs.

### Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

NNRTIs have been associated with skin rashes but less commonly with hypersensitivity reactions. The frequency of skin rashes associated with the various NNRTIs is similar, but it has been reported to be more frequent in patients treated with nevirapine. NNRTI-associated drug eruptions occurred in about 9-32% of clinical studies worldwide, with approximately 16% attributable to nevirapine.<sup>24</sup> About 5% of those initiated with nevirapine therapy developed more severe reactions such as fever and hepatitis.<sup>27</sup> In 0.3% of patients, severe reactions such as SJS and TEN developed after initiating the drug.<sup>27</sup> The hypersensitivity reaction develops between 10 days and 6 weeks after starting therapy. Severe skin rashes and rash-associated hepatitis occur more commonly in women. It has also been stated that severe hypersensitivity reactions occur more commonly in HIV-uninfected individuals who received therapy as post-exposure prophylaxis.<sup>24</sup>

### Protease inhibitors (PIs)

All the PIs have been documented as causing skin eruptions. The main PI implicated in the DHS is fosamprenavir. A possible explanation for this is that fosam-

prenavir is a sulphonamide. Fosamprenavir thus has the potential to cross-react with other sulphonamides, but information regarding this is currently limited.<sup>24,27</sup>

### Fusion inhibitors (FIs)

Enfuvirtide is administered by subcutaneous injection and the most frequent adverse effect is a local reaction at the site of the injection. Hypersensitivity reactions have been reported in less than 1% of patients who initiated therapy. It is usually

a delayed type of hypersensitivity reaction presenting with the usual symptoms and signs associated with the DHS. Desensitisation has been successful in some cases.<sup>24,27</sup>

### Drugs used to treat HIV-associated infections

Trimethoprim-sulphamethoxazole (TMP-SMX) is used in the treatment and prophylaxis of *Pneumocystis jirovecii* pneumonia (PJP) and has been a significant drug in the management of HIV-infected individuals. DH with TMP-SMX occurs in approximately 3-5% of HIV-uninfected but occurs in up to 60% of HIV-infected individuals.<sup>24,27</sup> TMP-SMX-associated life-threatening DH reactions occur in less than 1 in 10 000 of the general population, but in up to 4% of those infected with HIV.<sup>24</sup> TMP-SMX hypersensitivity presents mostly with a maculopapular or morbilliform skin rash with a fever and elevated transaminases. Fatalities, as a result of complications such as SJS and fulminant hepatic failure, occur rarely.

The high incidence of TMP-SMX hypersensitivity is secondary to multiple factors related to the altered metabolism of SMX in HIV-infected individuals. The reactive SMX metabolites that are generated by cytochrome P450 2C9 oxidation make the HIV-infected cell more susceptible to cell injury and death. The T cells interpret this as a 'danger signal' leading to an immune response which presents as a DH reaction.<sup>24</sup> HIV-infected individuals who have previously been diagnosed with a TMP-SMX hypersensitivity reaction have been successfully desensitised.<sup>28,29</sup>

HIV-infected individuals have a high risk of being co-infected with tuberculosis. The antituberculosis medications isoniazid (INH), pyrazinamide (PZA) and rifampicin are used as part of the first-line treatment against *Mycobacterium tuberculosis* and are the most implicated drugs for adverse effects.<sup>24</sup> HIV-infected individuals have a 20-fold increased risk of developing hypersensitivity drug eruptions compared with uninfected individuals.<sup>24</sup> The most common adverse events are skin rash and fever. DH skin rashes range from a morbilliform type rash to SJS and TEN. A study in Zambian children on an antituberculosis regimen that included thiacetazone showed that hypersensitivity skin reactions occurred within the first 2-4 weeks of commencing treatment.<sup>30</sup>

### Desensitisation

Therapeutic desensitisation or tolerance induction is 'the technique used to induce a state of unresponsiveness to the substance that continues as long as the drug is given.'<sup>23</sup> The aim is to enable a person who is allergic to a medication to tolerate treatment with that

drug.<sup>31</sup> The term desensitisation implies that the underlying mechanism is IgE-mediated, and thus the terms 'graded challenge' or 'tolerance induction' would be more applicable to DHS, particularly where TMP-SMX is concerned.<sup>29,31</sup> The starting dose should be low and gradually increased until full therapeutic doses are achieved, and should only be done in facilities that can manage severe reactions, especially anaphylaxis.<sup>26,29</sup>

### General management tips<sup>26</sup>

When a hypersensitivity reaction is suspected or occurs, the suspected causative drug should be withdrawn immediately. In mild hypersensitivity reactions antihistamines are the recommended treatment. In severe hypersensitivity reactions that correspond with anaphylaxis, adrenaline should be administered promptly via intramuscular or intravenous routes. Glucocorticosteroids have an anti-inflammatory effect that may reduce prolonged reactions or later relapses.

The management of SJS and TEN should preferably occur in an intensive care unit. Care should be taken to warm the environment, correct electrolyte disturbances, ensure high caloric intake and maintain strict antiseptic measures. Regular assessment of liver function is important as these patients are at risk of developing hepatic failure. The effectiveness of intravenous immunoglobulins is still being debated, despite their widespread use. Specialised nursing care and topical management have dramatically reduced morbidity and permitted more rapid healing of the skin lesions.<sup>26</sup> Avoidance of the specific drug that caused the hypersensitivity reaction is required.

### CONCLUSION

Allergic disease in HIV-infected patients is common, but the exact relationship between HIV and atopic disease needs further elucidation, and further studies are also required to assess the long-term outcomes in these patients.

HIV-infected individuals experience DH at a higher rate than the general population. It can be difficult to distinguish hypersensitivity reactions in an HIV-infected individual from an HIV-associated manifestation, but it is important to do so. In the developing world hypersensitivity reactions associated with HAART, TMP-SMX and antituberculosis drugs remain of great concern. A history of initiation of therapy followed by a DH reaction within 8 weeks remains the best diagnostic tool, as no specific laboratory test exists. Desensitisation is a treatment option if no alternative drug exists, except in the case of abacavir.

Managing patients with HIV and allergic disease can be complex and the input of both allergologist and infectious disease specialist is required in order to optimise these patients' treatment.

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