

Allergic Manifestations in AIDS

Pedro C. Avila and Jeffrey L. Kishiyama*

*Division of Allergy and Immunology, University of California, San Francisco,
432A Irving Street, San Francisco, CA 94143-0954*

HIV Disease and Immune Dysregulation

Hypersensitivity reactions and allergic manifestations of human immunodeficiency virus (HIV) infection have been observed since the beginning of the acquired immunodeficiency disease syndrome (AIDS) epidemic. Drug hypersensitivity remains the most visible and frequent untoward reaction, but chronic nasal symptoms and pruritic cutaneous disorders are also commonly observed allergic manifestations of HIV infection (1–3). Furthermore, a number of immunological derangements have been identified, which suggest an association between HIV infection and atopy. In this article, we review proposed pathophysiological mechanisms, diagnosis and management of the different clinical allergic disorders affecting HIV patients, and discuss controversial issues regarding immunotherapy in HIV disease.

HIV Disease and IgE Levels

HIV infection and its progression to AIDS is characterized by marked defects in immune regulation. As many as six investigator groups have observed elevations in total serum IgE in HIV-seropositive patients (3–8). Vigano et al. (7) compared total serum IgE from 58 vertically HIV-infected children to serum from 35 children with seroreversion, i.e., uninfected children born to infected mothers. Not only were IgE levels significantly increased in the HIV-infected children, but there was a statistically significant increase among AIDS patients compared to those with asymptomatic infection.

Elevated IgE levels were also associated with a worse clinical prognosis. One year later, the proportion of patients suffering a significant decrease in CD4⁺ cells was much higher among children with persist-

*Author to whom all correspondence and reprint requests should be addressed.

ently elevated IgE (14 of 19) compared to those with normal IgE levels (2 of 14) (7). In a large cohort of adult subjects (315 seropositive, 100 seronegative), Israel-Biet et al. (4) demonstrated a strong inverse relationship between IgE concentration and CD4⁺ cell counts. Their subgroup survival analysis of 52 patients with CD4⁺ counts <300/ μ L disclosed a 24-mo occurrence rate of AIDS of 83% in individuals with elevated IgE vs 44% in individuals ($n = 28$) with normal serum IgE levels (4).

Analysis of patients with elevated IgE levels has demonstrated both elevated total serum IgE and increased levels of antigen-specific IgE, measured by modified radioallergosorbant tests (RAST) for environmental aeroallergens. The prevalence of one or more positive RAST results for environmental antigens, including Bermuda and Timothy grasses, Common ragweed, English plantain, Oak pollen, cat and dog dander, *Alternaria*, house dust, and *Dermatophagoides farinae* (dust mite species), was 36–44% in patients with advanced HIV infection, compared to 7% in seronegative controls (6). They also found a relationship between advanced HIV infection with secondary infections and heightened IgE levels.

A variety of other immunologic disorders have been associated with elevated serum IgE levels, including atopic dermatitis, acute graft-vs-host disease following allogeneic bone marrow transplantation, Wiscott-Aldrich syndrome, Nezelof syndrome, DiGeorge syndrome, and selective IgA deficiency. T-cell dysregulation is a common feature shared among these syndromes and HIV infection, lending credence to the hypothesis that the elevated serum IgE levels are related to impaired cellular immunomodulation. Production of other antibody isotypes may also be dysregulated, as exemplified by polyclonal IgG elevation and aberrant polymeric IgA1 rheumatoid factor.

The lack of concordance between elevated IgG and high IgE levels suggests that isotypic-specific mechanisms of dysregulation may be involved in HIV-infected patients (6). The elevated IgG levels, secondary to polyclonal B-cell activation, seem to reflect chronic immune system activation. Polyclonal B-cell activation may also be induced through increased interleukin (IL)-6 production. HIV-gp120 envelope protein may also act as a superantigen to all B-cells expressing VH3⁺ surface immunoglobulin, stimulating immunoglobulin secretion by large numbers of B-cells, in an unrestricted, antigen-nonspecific manner (9,10).

HIV and Cytokines

Several different mechanisms have been proposed to explain the elevated levels of serum IgE. Carini et al. (11) implicated IgE-binding factors, which are spontaneously produced by mononuclear cells in

HIV-infected subjects and can modulate IgE production. Others suggest that altered or dysregulated cytokine production leads to increased IgE production (12). It is well known that IL-4, IL-5, and IL-6 play a role in the development of allergic disease. IL-4, IL-5, and IL-6 modulate B-cell activity, antibody responses, and eosinophil function. IL-4 is the crucial factor for B-cell isotype antibody switching, initiating a shift from IgM to IgE and IgG1 synthesis. It also functions as a growth factor for mast cells and induces the upregulation of CD23, the low-affinity receptor for the Fc portion of IgE on B-cells and macrophages.

IL-5 is a major stimulus for eosinophil growth, differentiation and activation. In addition to regulating eosinophil-mediated inflammation, it also costimulates B-cell growth, and together with IL-6 can upregulate an IL-4-induced IgE response. IL-6 has been shown to be elevated in numerous HIV-infected culture cell lines and in vitro cultures of peripheral blood mononuclear cells (PBMCs). The observed elevated IL-6 production can be induced by gp41 envelope protein (13), gp120 synthetic peptides (14), or occur spontaneously (15).

The interest in cytokine regulation of humoral and cell-mediated immunity has practical significance in host defense against microbial infection. Analogous to a popular murine T-cell paradigm, individual human T-cells tend to produce cytokines in discrete, well-defined patterns after antigen stimulation. T-helper (Th)-cell cytokine production has been dichotomized into type-1 (Th1) and type-2 (Th2) responses. Th1 responses are defined by high IL-2 and interferon-gamma (IFN- γ) production, but low IL-4, IL-6, and IL-10 synthesis. Th2 responses are characterized by an opposing profile, with enhanced generation of IL4, IL-5, IL-6, and IL-10, but low IFN- γ , and IL-2 secretion. Beyond cytokine gene expression, the Th1/Th2 designation implies differences in immune response by each T-cell phenotype. The Th1 response predominates in cell-mediated immunity, whereas Th2 responses are more important in humoral immunity (16). These functionally dichotomous classifications are artificially rigid and probably represent functional extremes. A revised paradigm allows for uncommitted T-cells, designated Th0 clones, which synthesize both Th1- and Th2-type cytokines.

Some pathogens are controlled more effectively by antibody-mediated responses, whereas other infections require cytotoxic T-lymphocyte activity for containment. The nature of the infectious agent and its interplay with the host genetics determines the cytokines produced during the effector phases of immune responses, thereby orchestrating the appropriate balance of humoral and cell-mediated immunity. For example, viral and mycobacterial pathogens tend to promote Th1 responses, whereas parasites and helminths produce well-characterized Th2 responses.

A recent hypothesis by Clerici and colleagues (17,18), proposes that a functional switch in T-cell phenotype, from Th1 to Th2 pattern of cytokine production, is associated with diminished cell-mediated immunity and progressive HIV disease. Their theory was developed to explain the impaired memory responses to recall antigens observed in lymphocytes from asymptomatic HIV-infected individuals. Others had already established that impaired cell-mediated immunity, assessed by delayed-hypersensitivity skin test responses to recall antigens, such as tetanus, mumps, or *Candida* antigens, correlates with progression of HIV disease. Likewise, in vitro assays demonstrated impaired cell-mediated responses in lymphocytes from HIV-infected subjects. Using IL-2 production and lymphocyte proliferation as markers of cell-mediated immune reactivity, Clerici et al. (19) found diminished responses were associated with increased in vitro IL4 synthesis. Additionally, lymphocytes from patients with intact cellular responses demonstrated predominantly IL-2 production. In other words, the state of HIV-related immunodeficiency seemed to correlate with changes in cytokine expression by immune cells.

To explore the biologic relevance of these cytokine-mediated responses, they examined an in vitro model of HIV-induced programmed T-cell death. They 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 (19). These cytokine-mediated effects on cell death provided a mechanism for the immunopathogenesis of T-cell depletion and HIV-progression. Moreover, overproduction of Th2-type cytokines can also suppress cellular immunity and IFN- γ production through reciprocal, immunocounterregulatory mechanisms.

In a mouse model of murine retrovirus-induced acquired immunodeficiency, cytokine dysfunction and a Th1 $\rightarrow$ Th2 shift also appear crucial to the development of murine AIDS (MAIDS) (10,20). Gazinelli and colleagues showed that resistant strains of mice demonstrate an increase in IFN- γ and IL-2, whereas susceptible strains produce increased IL-4 and IL-10 after retroviral infection (21). Treatment with cyclosporin A, which inhibits cytokine production, and IL-12, which promotes a Th1 response, abrogates the development of MAIDS (10).

Despite early enthusiasm for Clerici and colleagues' Th1 $\rightarrow$ Th2 hypothesis, not all experimental systems have yielded evidence for the dichotomous cytokine response patterns in HIV infection. Graziosi et al. (22) found no evidence of a Th2 pattern predominance among constitutively expressed cytokines ex vivo in cross sectional or longitudinal analysis from HIV-infected individuals. Examining cytokine production by activated peripheral blood mononuclear cells and T-cell clones, Maggi et al. (23) found a shift from Th1 $\rightarrow$ Th0 phenotype, but

also discovered that HIV preferentially replicates in Th2-type T-cells, potentially causing a preferential depletion of CD4⁺ Th2 cells in advanced phases of disease.

Differences in model system, the time-course of cytokine production, or the clinical status of the subjects may have contributed to the discordant reports (24). Cytokines are produced by a host of immune and nonimmune cells, and several groups have identified CD4⁺, CD8⁺ T-cells with Th2-like cytokine production with reduced cytolytic activity (25,26). Alternatively, the heterogeneity of responses may merely reflect the diversity of immune responses in HIV infection or the complexities of T-cell activation. Indeed, the Th2 bias may be more of an epiphenomenon than a primary pathogenetic mechanism in clinical HIV infection. In summary, the Th1→Th2 switch is an attractive theory that could link the immunopathogenesis of HIV infection, IgE production, and the development of allergic diathesis, but it remains controversial and awaits confirmation by future investigations.

Atopy and Allergic Manifestations

It has been observed that allergic diathesis is more prevalent in HIV-infected patients compared to noninfected individuals. The increased incidence of hypersensitivity reactions to drugs is well recognized (27). However, an increased prevalence of atopic airways disease has been difficult to demonstrate. The frequently cited references are difficult to interpret owing to lack of comparable control groups, evidence of reporting bias, utilization of inadequately described survey instruments, or lack of diagnostic criteria for allergic disorders (28,29). Despite the methodological shortcomings, the reported data demonstrate correlations between clinical symptoms and certain laboratory findings, providing some insight about the pattern of atopic disease in HIV-infected populations.

In a survey of 45 HIV-infected male patients treated in an ambulatory AIDS clinic in San Francisco, 41% reported a history of allergic rhinitis, allergic conjunctivitis, urticaria, or extrinsic asthma. This compares to a prevalence of allergic rhinitis (20%) and asthma (5%) in the general population. Moreover, patients with advanced HIV disease were twice as likely to have positive RAST tests, nasal eosinophilia, abnormal sinus radiographs, or seek medical attention for allergic symptoms than less advanced or noninfected control patients (6).

In a study of HIV-infected patients with rhinosinusitis treated at an inner city Bronx hospital infectious disease clinic, the incidence of allergic skin test reactivity to common aeroallergens, was unexpectedly high. Twenty-three of 32 (72%) of these patients demonstrated IgE-sensitivity to two or more aeroallergens, on a test panel of grass, molds,

trees, ragweed, cockroach, and dust mite allergens. The prevalence of atopy in a comparable group of non-HIV-infected patients with rhinosinusitis was 24%, whereas the prevalence of allergen-specific serum IgE in nonatopic normal control, age- and sex-matched from the same area, was 12.5% (30). The overall incidence of sinusitis in this population was high, 41% overall in HIV-infected patients and 64% in the subgroup with AIDS. Small et al. (30) concluded that newly acquired atopy could precede or predispose the development of sinusitis in this population (30).

Management of Rhinosinusitis in HIV-Infected Patients

The bacteriology of chronic sinusitis in HIV-infected patients was recently characterized by Tami (32), who examined culture results from samples obtained during surgery or rhinoscopic procedures. The etiologic agents were identified in 22 of 32 patients with chronic sinusitis (69%) (32). The most commonly encountered organisms were coagulase-negative staphylococcus (37%), *Pseudomonas aeruginosa* (16%), *Streptococcus pneumoniae* (9%), *S. viridans* (6%), *Aspergillus fumigatus* (6%), and *Staphylococcus aureus* (3%) (32). Unusual pathogens have been reported in HIV-related chronic sinusitis, such as cytomegalovirus, *Enterobacter* sp., *Klebsiella pneumoniae* and fungi. The prevalence of *P. aeruginosa* is surprisingly high, but common bacterial species, including *Staphylococcus*, *Pneumococcus*, *Haemophilus influenzae*, and anaerobic bacteria are still considerations.

The diagnostic evaluation may include sinus computed tomography (CT) and nasopharyngoscopy. The sinus CT scan is superior in defining the extent, sites of infection, anatomical aberrations that might contribute to impaired drainage, and patency of the osteomeatal complex. During nasopharyngoscopy, purulent drainage may be observed around the sinus ostia and collected for culture. Sinusitis may become refractory to therapy when CD4⁺ count falls below 200/ μ L (31,32).

Medical management of chronic sinusitis consists of antibiotics, decongestants, and anti-inflammatory therapy. In acute sinusitis, amoxicillin or sulfamethoxazole/trimethoprim is often chosen for primary treatment, but amoxicillin/clavulanate (Augmentin) or oral cephalosporins, such as cefuroxime (Ceftin) or cefpodoxime (Vantin), are often better choices. Oral antibiotics are usually given for a minimum of a 3 wk duration. For treatment of chronic sinusitis, the antibiotic spectrum should include expanded coverage for *S. aureus*, *P. aeruginosa*, and anaerobes. Initial empirical antibiotic therapy using Ciprofloxacin and clindamycin is a good empirical choice and should be continued for 4–6 wk. In the face of refractory sinusitis in HIV patients, one should strongly consider ENT consultation for direct

aspiration from sinus outflow tracts via direct rhinoscopy, since nasopharyngeal cultures or nasal swabs are unreliable for microbiological determination of sinus pathogens. Antral puncture, although traditional and effective, may be unnecessarily invasive (32).

Owing to the high prevalence of nasal mucosal edema caused by underlying allergic or nonallergic rhinitis, the use of adjunctive decongestants and anti-inflammatory drugs, in addition to antibiotics, is essential for optimal therapy and may minimize recurrent infection. Systemic pseudoephedrine, phenylephrine, or phenylpropanolamine is useful. Topical decongestants can be used in the first 3–4 d of therapy, but prolonged use can lead to rebound mucosal edema (rhinitis medicamentosa). In addition to enhancing physiologic mucociliary function, large-volume nasal saline lavage may be helpful in loosening or evacuating inspissated mucus. Topical nasal corticosteroids safely reduce chronic mucosal inflammation and edema, and can be used long term. Antihistamines can be counterproductive, since their anticholinergic effects may thicken mucus and impair drainage.

If oral antibiotics fail, iv formulations may be required. In some instances, endoscopic sinus surgery may be necessary to attain adequate sinus drainage and obtain specimens for culture. In patients with significant immune impairment, curative surgery may not represent an attainable goal, but may lead to substantial symptomatic relief and improvement in quality of life (32,33).

Drug Hypersensitivity

In HIV-infected patients, drug reactions are frequent. As many as 65–83% of patients will suffer from adverse reactions to sulfonamide therapy (34–36). Reactions occur more often in the late stages of HIV disease (AIDS or $CD4^+ < 200/\mu L$) (37) and are clinically manifested by fever, rash, anaphylactic-like reactions, neutropenia, thrombocytopenia, or anemia. Typically, the cutaneous rash presents as a morbilliform, pruritic eruption, developing within 7–10 d of therapy. More rarely, Steven-Johnson syndrome, toxic epidermal necrolysis, hepatitis, interstitial pneumonitis, or nephritis can occur. Because these reactions mimic hypersensitivity reactions seen in non-HIV-infected patients, these reactions have often been assumed to have an allergic or immunologic basis.

The potential pathogenetic mechanisms underlying these reactions, however, are poorly understood and may not be limited to allergic hypersensitivity. In many HIV-infected patients, treatment with multiple medications increases their risk for drug toxicity and drug interaction. The determination of pathophysiologic mechanisms, i.e., allergic hypersensitivity vs drug toxicity, is important for its prognos-

tic implications and avoidance of adverse drug reactions (38). First we review the differences between immunologic and nonimmunologic drug reactions, and then we apply these concepts to commonly occurring sulfonamide reactions seen in HIV-infected individuals.

Allergic or immune-mediated reactions involve specific antibodies or sensitized T-cells, which are reactive to a drug or its metabolites, in native or haptened form. These reactions can be manifested by IgE-mediated immediate hypersensitivity (e.g., urticaria, anaphylaxis), autoreactive cytotoxic antibody reactions (e.g., immune cytopenias), immune complex formation with complement activation (serum sickness), or lymphocyte-mediated delayed hypersensitivity reactions (e.g., contact dermatitis). They have several features that help distinguish them from other types of adverse reactions:

1. Allergic reactions usually occur in a small percentage of patients receiving the drug;
2. The clinical manifestations do not resemble the expected pharmacologic actions of the medication, but resemble the aforementioned immune-mediated reactions;
3. An initial period of sensitization is required;
4. They are reproducible with minute amounts of the drug or compounds with similar crossreacting chemical structures; and
5. Blood or target organ eosinophilia may be present (39).

Nonimmunologic drug reactions, on the other hand, can be owing to side effects, which are predictable and related to pharmacologic effects, toxic effects, which are often related to excessive dosage, or could be unpredictable and idiosyncratic.

Among all the drugs that cause reactions in HIV patients, the sulfonamides are the most commonly implicated and best studied. Trimethoprim-sulfamethoxazole (TMP-SMX) is the agent of choice for *Pneumocystis carinii* pneumonia (PCP) treatment and prophylaxis; and sulfadiazine is used for cerebral toxoplasmosis. Most of the TMP-SMX adverse reactions are cutaneous (75%) and may ensue in up to 65–83% of HIV patients, 10 times the rate seen in noninfected individuals (34–36). Usually the HIV-infected patients develop skin rash, with or without fever. The cutaneous manifestations can be erythematous, maculopapular or morbilliform rash (74%), pruritis, generalized erythroderma, or urticarial rash (40).

Two observations suggest that HIV-induced pathophysiology causes the increased drug reactivity rather than the drugs themselves. First, a retrospective comparison of trimethoprim-sulfamethoxazole (TMP-SMX) reactions revealed a 65% incidence of adverse reactions in AIDS-related PCP compared to 12% incidence in non-HIV-infected PCP cases. The observed incidence in the non-HIV-infected PCP groups was not statistically different from that observed in the general public (36).

Second, the tendency for HIV-infected patients to develop fever and skin rash to multiple drugs of nonrelated chemical classes suggests that HIV causes the enhanced drug reactivity.

Viral infections can cause an increased incidence of cutaneous drug reactions. A high rate of cutaneous reactions to ampicillin is well documented in mononucleosis syndromes caused by Epstein-Barr virus (EBV) (42) or Cytomegalovirus (CMV) infections (43). The immunomodulatory effects of EBV may be related to its B-cell tropism and effects on cytokine production (44). In fact, the morbilliform eruption seen with sulfonamides and HIV infection is remarkably similar to that seen with ampicillin and EBV-infection. It is tempting to speculate that concurrent or subacute EBV or CMV infections occur in HIV-seropositive patients with drug rash, but this has not been proven. Other disorders with immunological activation, including chronic lymphocytic leukemia and allopurinol-treated gout, may also be associated with increased reactions to ampicillin (45,46).

Less commonly, sulfonamide-induced reactions may present as cytopenias, elevation of transaminases; and rarely, Steven-Johnson syndrome, erythema multiform, exfoliative erythroderma, toxic epidermal necrolysis, and anaphylaxis-like reactions. A severe anaphylaxis-like reaction consisting of immediate fever, rash, hypotension, pulmonary edema, and hypoxemia has been described (47–49). These episodes may be rapid and occur on re-exposure 2–3 wk after discontinuation of an initial course of TMP-SMX. They cannot be predicted, however, on the basis of previous reactions. A few of these patients have been successfully desensitized (50).

These presentations invoke suspicion of immunologic mechanisms. IgE, IgG, IgA, and IgM antibodies to sulfamethoxazole and its metabolites have been found in most HIV patients with cutaneous reactions, but the clinical significance of these serum antibodies is not known (51,52). Despite the HIV-induced dysregulation of total serum IgE and IgG, evidence of immunoglobulin deposition in cutaneous reactions has not been seen (53). Other sulfa-containing medications, including TMP-dapsone, sulfadioxine, and sulfadiazine, have been associated with cutaneous reactions in HIV infection, but at lower rates.

Recent studies of the sulfa metabolites and their haptens have provided further insight into possible mechanisms of TMP-SMX adverse reactions (54). Sulfonamides can be metabolized through several enzymatic pathways. Conjugation of sulfonamide metabolites to glutathione leads to nonimmunogenic molecules, which are excreted. Metabolites undergoing alternative pathway cytochrome P₄₅₀ enzyme-mediated N4-oxidation, however, become allergenic haptens. Glutathione is an important antioxidant; and glutathione levels in plasma, bronchoalveolar lavage fluid, and cells is reduced in HIV-infected patients (55).

It has been hypothesized that genetically slow acetylators or glutathione-deficient HIV-infected patients may shunt a larger percentage of their sulfonamide metabolism toward the N⁴-oxidative pathway, generating increased amounts of immunogenic metabolites (51).

Antibodies directed toward these immunogenic sulfonamide haptens have been detected in HIV-infected patients (56). Moreover, a recent prospective study has suggested that the presence of anti-SMX IgG antibodies, before sulfonamide desensitization, predicts failure of the procedure and may be involved in the pathogenesis of adverse reactions (57). Further studies on the immune response to haptens containing sulfa drugs and its metabolites, as well as prospective evaluations of the predictive values of laboratory tests, are needed.

Koopmans et al. (38) reviewed the evidence suggesting that a nonimmunologic process is accountable for the increased incidence of sulfonamide reactions. There seems to be evidence of a dose-dependent relationship, which is not typically seen in true allergic reactions. In febrile or cutaneous reactions to sulfonamides, some patients will tolerate continued administration of the medication, either after a short interruption, at a lower dose, or with antihistamine/corticosteroid coadministration. Re-exposure without recurrence of symptoms, which is a commonly observed phenomenon, would not be easily accomplished if immune-mediated mechanisms were present.

According to the theory proposed by Shear and others (58–60), toxic metabolites, not immunogenic products, cause adverse drug reactions in HIV-infected patients. Toxic hydroxylamine metabolites are generated in hepatic microsomes through cytochrome P₄₅₀ metabolism of SMX. The overall production of these hydroxylamines is similar in HIV-infected and noninfected controls, but HIV-infected patients may be more susceptible to their toxic effects. Experimental in vitro models suggest that hydroxylamines are more cytotoxic to lymphocytes from patients with a history of adverse reactions to SMX, than to lymphocytes from healthy donors. Supplemental glutathione antagonized this in vitro cytotoxic effect (60). This same mechanism may explain reactions to other drugs, since metabolism of dapsone, phenytoin, carbamazepine, valproate, and phenobarbital generates analogous toxic hydroxylamine metabolites (61,62).

Infection with HIV may also affect the rates of other metabolic pathways. Lee et al. (63) detected differences in drug acetylation, demethylation, and 8-hydroxylation among patients at different stages of HIV disease. Although limited by its cross-sectional design, there were differences noted among acutely ill AIDS patients and healthy controls. It has been well established, that acetylation phenotype determines the risk of side effects from procainamide and hydralazine. The

clinical relevance of genetic or acquired differences in drug metabolism in HIV infection, however, remains speculative.

Management of Drug Reactions in HIV Infection

In general, precautionary measures can decrease the incidence of allergic reactions. Drugs should be prescribed appropriately, and if possible, those drugs with a reputation for causing allergic reactions should be avoided. Many drugs have been shown to cause severe reactions in HIV patients, including but not limited to clindamycin, pentamidine, dapsone, ketoconazole, dicloxacillin, didanoside, erythromycin, maloprim, phenobarbital, phenytoin, rifampin, sulfadiazine, sulfadoxine-pyrimethamine, SMX-TMP, thiacetazone, thalidomide, atovaquone, and valproic acid. Unfortunately, there are few good test reagents for determining drug hypersensitivity. With the exception of penicillin major and minor determinants, and high-mol-wt proteins (e.g., heterologous sera, foreign proteins, monoclonal antibodies, insulin), no in vivo or in vitro laboratory test can accurately predict drug reactions.

Once an adverse reaction occurs, one should evaluate the risks and benefits of continuing the drugs and treating the reactions vs discontinuing the suspected medications. Such a decision-making process is based on the severity of the reaction, the probable mechanism involved, and the availability of alternative therapies. If a drug has to be stopped because of adverse reactions, consultation with an expert in drug allergy with experience in diagnostic testing, test dosing, and desensitization is warranted (39).

If there is a strong probability of a hypersensitivity reaction and no alternative medication exists, consider drug desensitization. There are two types of desensitization that can be applicable to some drug reactions. First, in cases of probable life-threatening IgE-mediated anaphylaxis, protocols have been developed for acute desensitization. This involves administration of very minute dosages, with progressively larger amounts of drug given at 15-min intervals. It is believed that gradual univalent haptentation causes antigen-specific mast cell desensitization. After successful desensitization, uninterrupted full-dose oral or parenteral therapy can be administered. Acute desensitization carries significant risk of life-threatening reaction, should be performed in an intensive care setting, and should be supervised by an allergy/immunology expert familiar with the procedure. No premedication has consistently proven effective in preventing severe, antigen-induced immediate hypersensitivity reactions (51).

A second type of "desensitization" protocol has been developed for sulfonamide-induced febrile-cutaneous reactors. This procedure is

distinct from the previously described acute desensitization, and its mechanisms of action is less well understood. This procedure also involves ascending doses of drug administration, but over hours to days, rather than minutes. There is no immunologic mechanism that potentially explains its effectiveness. Since the first described protocol for desensitization to sulfa in HIV patients (64), many others have followed, and it has been successful in hundreds of HIV patients (50). Desensitization has been successful in cases of fever, rash, and cytopenic reactions (50,65–68).

Either desensitization procedure is contraindicated in patients who suffered life-threatening reactions, such as Steven-Johnson syndrome, toxic epidermal necrolysis, severe hepatic necrosis, severe agranulocytosis, exfoliative dermatitis, and fibrosing alveolitis. Desensitization schemes for other drugs, used in HIV infection have also been successfully employed, as in the case of zidovudine (69), pentamidine (70,71), and acyclovir (72).

Other Manifestations

A few patients with AIDS-related complex (ARC)/AIDS were found to have very high IgE levels, hypereosinophilia in the absence of parasitic disease, chronic dermatitis, and recurrent staphylococcal infections. These features are remarkably similar to the Hyper-IgE syndrome (Job's syndrome), a rare primary immunodeficiency disorder. Paganelli et al. (73) described a cohort of nine such patients, representing a distinct expression of HIV disease. Their clinical presentation includes chronic diffuse pruritic dermatitis with lichenification, mucocutaneous candidiasis, subcutaneous abscesses caused by *S. aureus*, and severe viral infections.

Hypereosinophilic syndrome was described in an HIV-infected patient with diffuse cutaneous eruption, fever, eosinophilia, and elevated serum IgE (74). The patient suffered from advanced HIV disease, with a marked depletion of CD4⁺ cells. Although eosinophilic folliculitis is a common dermatosis reported in HIV-infected patients with CD4 count <300/ μ L (75,76) this patient had additional findings of angioedema, mucosal ulcerations, and bone marrow infiltration by mature eosinophils. Unlike non-HIV-related idiopathic hypereosinophilia syndrome, he had no clinical evidence of other visceral infiltration. He had elevated serum levels of IL-5, which has also been seen in idiopathic hypereosinophilia syndrome, parasitic infections, and tryptophan-induced eosinophilia-myalgia syndrome.

HIV Infection and Immunotherapy: A Concern

Immunization as prophylaxis for infectious disease and allergen immunotherapy injections for immediate hypersensitivity are effective and widespread therapeutic interventions. Both therapies utilize exog-

enous immunogens to induce protective immune responses. It may not always be clear, however, whether a cell-mediated or humoral response predominates and ultimately provides protection. Furthermore, a quandary has arisen concerning these immunologic therapies.

It has been the practice of many to terminate allergen immunotherapy in HIV-infected patients. These decisions have been based on a theoretical concern about immune activation and its impact on HIV infection. In vitro lymphocyte activation has been shown to enhance HIV replication. Fauci (77) strongly believed that in vivo immune activation may not only propagate the infection, but lead to the destruction of lymphoid tissue and ultimately, profound immunosuppression (78).

Although there are no data regarding allergen immunotherapy, recent in vivo studies of influenza immunization have shown that influenza virus vaccination activates HIV replication. Measurement of HIV-1 ribonucleic acid (RNA) in the plasma, and peripheral blood lymphocytes, before and after vaccination, demonstrated transient increases in viral load for 4 wk, mainly in those patients with higher CD4⁺ count (>500/ μ L) and those with good influenza virus-antibody response. Profiles of lymphocyte subsets were not altered, and no clinical adverse outcome was noted after 12 wk of follow-up (79,80). Recent studies show that specific-antigen stimulation with tetanus vaccine induces transient increase in plasma viral load, lymph node expression of HIV mRNA, and the lymph node dendritic cells have an 100-fold increase in their ability to infect normal OD4⁺ cells in vitro (81,82). For HIV infection, plasma HIV-RNA levels correlate with tissue and systemic viral load and disease prognosis (83).

The primary mechanism of action of allergen immunotherapy has not been elucidated, but multiple immunologic responses have been observed, including production of "blocking" IgG antibodies, generation of antigen-specific T-suppressor cells, and change in lymphocyte cytokine profiles. The immunopathological significance of immunotherapy-induced in vivo immune activation remains indeterminate, but PBMCs isolated from normal volunteers, are 10–100 times more susceptible to HIV-1 infection in vitro following antigenic stimuli (76). Until further studies better characterize the effects of allergen immunotherapy on the natural history of HIV infection, it is not recommended in HIV-infected individuals.

Conclusion

During the progression of HIV infection, patients demonstrate immune dysregulation, and may develop increasing levels of serum IgE and other markers of atopic disease. In particular, elevated IgE levels have been correlated with a poorer prognosis. Patients with HIV

infection have a higher incidence of drug hypersensitivity, sinusitis, and skin test reactivity to aeroallergens, but the exact prevalence of atopic airways disease has been difficult to ascertain. Prevalence studies of allergic rhinitis, asthma, urticaria, and allergic eczema in HIV-infected patients are hard to interpret owing to methodological limitations. Allergic manifestations can affect patients at any stage of HIV infection, but may herald evolution to AIDS in late stages. Up to 70% of HIV-infected patients develop drug reactions, which complicates management of opportunistic infections, but desensitization has been successful for many drugs. There is some evidence suggesting that immunologic and/or toxic mechanisms may underlie the pathogenesis of the frequently occurring drug reactions. In vitro studies have shown that antigenic stimulation induces T-cell proliferation and facilitates HIV replication. Recent in vivo studies demonstrate transient increases in the HIV viral load with vaccination and raise concern about the possibility of hastening HIV disease progression with allergen immunotherapy.

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