
HIV: Practical implications for the practicing allergist-immunologist

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Objectives: To review the effects of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) on allergic diseases and discuss the clinical, pathophysiologic, diagnostic, and therapeutic challenges unique to HIV-infected patients receiving highly active antiretroviral therapy (HAART).

Data sources: The MEDLINE and OVID databases were searched to identify pertinent articles using the following keywords: HIV, AIDS, IgE, allergic rhinitis, adverse drug reaction, asthma, chronic obstructive pulmonary disease, food allergy, and immunization. References from the chosen articles were also examined.

Study Selection: Articles were selected based on their relevance to the subject matter and currency.

Results: Human immunodeficiency virus infection causes immunologic alterations that ultimately lead to cell-mediated immune deficiency. In addition, the immune dysfunction caused by HIV also increases the likelihood of developing allergic and other immune-mediated diseases in many patients. HAART is associated with reconstitution of immune system function. While offering protection against infection, immune reconstitution also can provoke immunopathologic conditions. Patients infected with HIV show an increased prevalence of allergic rhinitis, adverse drug reactions, and noninfectious pulmonary complications. The pathophysiology of HIV infection is associated with unique clinical, diagnostic, and therapeutic considerations when treating allergic diseases in HIV-infected patients.

Conclusions: With the use of HAART and the subsequent decrease in infectious complications, HIV-infected patients now live longer and experience common chronic diseases. Evaluation of HIV-infected patients with rhinitis, asthma, and adverse drug reactions may become more frequent as HAART continues to extend the life expectancy of patients living with HIV. Understanding the interactions between HIV and these conditions can facilitate a knowledgeable approach to treating an HIV-infected patient.

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INTRODUCTION

Recent advances have made a significant impact on the management, outcome, and long-term prognosis of human immunodeficiency virus (HIV)-infected patients.¹ Suc-

cessful antiretroviral therapy is associated with dramatic decreases in acquired immune deficiency syndrome (AIDS)-defining conditions and their associated morbidities and mortality. With the advent of highly active antiretroviral therapy (HAART), HIV-infected patients are living longer and experiencing commonly seen chronic diseases. A high incidence of clinical symptoms suggestive of immunoglobulin E (IgE)-mediated allergic disease occurs in individuals infected with HIV. The practicing allergist-immunologist should be aware of the diverse allergic conditions with which HIV-infected patients may present and should be prepared to use therapies to decrease morbidities and improve quality of life for these patients, whose life expectancies are continuing to improve as new HIV-specific therapies are developed.

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GENERAL CHARACTERISTICS OF HIV INFECTION

Epidemiology

The global HIV epidemic continues to spread and affect communities throughout the world. According to estimates by The Joint United Nations Programme on HIV/AIDS and the World Health Organization, 33.3 million people were living with HIV at the end of 2009.² Of these, 2.5 million were children younger than 15 years of age. In 2009 alone, 2.6 million people were newly infected, and 1.8 million AIDS-related deaths occurred. Globally, more than 16 million children younger than age 18 have lost 1 or both parents to HIV.

Ninety-three percent of people living with HIV live in developing countries, with more than two thirds living in sub-Saharan Africa. It is estimated that at the end of 2006, more than 1.1 million people in the United States were living with HIV. In addition, approximately 56,000 new HIV infections were diagnosed in the United States annually from 1996 through 2006.³ Despite these trends, the number of AIDS-related deaths in the United States in 2007 (14,581) was 69% lower than in 1994 (47,100). This favorable trend is in large part attributable to the increased availability and use of anti-retroviral treatments. As a result of the decrease in the death rate, the prevalence of HIV-infected patients has increased, leading to an extension in the lifespan of people living with HIV. The World Health Organization estimates that more than 7.2 million life-years have been added in Western Europe and North America alone because of antiretroviral therapy.²

Immunopathogenesis

HIV infection is caused by human RNA retroviruses, HIV type 1 (HIV-1) and, less commonly, HIV type 2 (HIV-2), a related virus that is rare in the United States but more common in West Africa. Patients infected with HIV show complex immunological alterations. The HIV infection ultimately causes progressive CD4+ T-cell destruction and resultant impaired cell-mediated immunity by several mechanisms. These include HIV-induced apoptosis, direct viral cytopathic effect, apoptosis secondary to chronic immune activation, antibody-dependant cell-mediated cytotoxicity, and CD8+ T-cell cytotoxicity against HIV-infected cells.⁴ The loss of

CD4+ T cells results in the development of opportunistic infections, increased risk of malignancy, and other conditions that are seen in patients with defects in cell-mediated immunity. In addition, HIV gene transcription is linked to the activation of T cells by antigen or cytokine stimulation. Thus, the recurrent infections seen in AIDS patients stimulate increased HIV production and promote infection and destruction of additional cells.

B-cell dysfunction also occurs in HIV infection and was among the first specific lymphocyte abnormalities to be described in patients with AIDS.⁵ Loss of CD4+ helper T cells negatively affects B cell activation. In addition, activation of apoptosis pathways leading to B cell depletion has been described in HIV-infected patients. Many features of B cell dysfunction in HIV disease also suggest a role for polyclonal B cell activation, leading to hypergammaglobulinemia, increased autoantibodies, and increased B cell malignancies.⁶ Irreversible loss of CD27+ memory B cells also has been reported. The overall effect of these findings leads to a decreased capacity to proliferate in response to B cell stimuli, a decreased capacity to respond to neo- and recall-antigens, and a decreased capacity to generate antigen-specific memory B cells.⁶

Treatment

Major advances in the treatment of HIV infection have been made since effective antiretroviral regimens first appeared in the mid-1990s. Although a detailed discussion on HIV treatment is outside the scope of this review, having general knowledge of current HIV antiretroviral treatment options can aid in evaluating and managing HIV patients with allergic diseases. Consideration of treatment specifics in an HIV-infected patient depends on careful assessment of the patient's clinical history, current signs and symptoms, HIV RNA level, CD4+ cell count, associated comorbid conditions, and the patient's commitment to lifelong therapy.⁷

Available antiretroviral agents target different steps in the viral replication cycle. These agents include nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, an integrase inhibitor, a fusion inhibitor, and an entry inhibitor (Tables 1 and 2). The NRTIs prevent HIV reverse transcrip-

Table 1. Antiretroviral Drugs Used in the Treatment of HIV Infection

Nucleoside reverse transcriptase inhibitors	Nonnucleoside reverse transcriptase inhibitors	Protease inhibitors	Integrase inhibitor	Fusion inhibitor	Entry inhibitor
Abacavir	Efavirenz	Amprenavir	Raltegravir	Enfuvirtide	Maraviroc
Didanosine	EtravirineM	Atazanavir			
Emtricitabine	Delavirdine	Darunavir			
Lamivudine	Nevirapine	Fosamprenavir			
Stavudine		Indinavir			
Tenofovir		Lopinavir			
Zidovudine		Nelfinavir			
		Ritonavir			
		Tipranavir			

Table 2. Combination Antiretroviral Drugs Used in the Treatment of HIV Infection

Trade name	Generic components	Drug class
Atripla (Bristol-Myers Squibb, New York, New York and Gilead Sciences, Foster City, California)	Emtricitabine, tenofovir, and efavirenz	NRTI, NRTI, and NNRTI
Combivir (GlaxoSmithKline, Research Triangle Park, North Carolina)	Lamivudine and zidovudine	Both NRTIs
Epzicom (GlaxoSmithKline)	Abacavir and lamivudine	Both NRTIs
Trizivir (GlaxoSmithKline)	Abacavir, zidovudine, and lamivudine	All 3 NRTIs
Truvada (Gilead Sciences)	Tenofovir and emtricitabine	Both NRTIs
Kaletra (Abbott, Chicago, Illinois)	Lopinavir and ritonavir	Both PIs

Abbreviations: NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

tase from adding new nucleotides to the growing HIV complementary DNA (cDNA) chain, thereby terminating HIV cDNA synthesis. The NNRTIs block viral reverse transcriptase by an alternative mechanism and likewise terminate the synthesis of HIV cDNA. Protease inhibitors block HIV protease and are also used to prevent HIV polyproteins from being cleaved into essential functional protein products. The integrase inhibitor (raltegravir) blocks HIV integrase from inserting the viral genome into the DNA of the host cell. The fusion inhibitor (enfuvirtide) binds to viral envelope glycoproteins and inhibits viral fusion with the target cell membrane. Finally, the entry inhibitor (maraviroc) blocks the HIV coreceptor CCR5 and thereby prevents viral fusion with the target cell membrane. Current evidence supports the use of a combination of two NRTIs/NNRTIs together with a third agent from another class.⁸

Highly active antiretroviral therapy should be considered for all HIV-infected infants because of rapid disease progression in this age group. In adults and children older than 12 months, HAART should be initiated when the CD4+ T cell count is less than 500 cells/mm³, with some even favoring initiation at CD4+ T cell counts above 500 cells/mm³, given recent evidence suggesting that the survival benefit may be increased with early HAART initiation.¹ Highly active antiretroviral therapy also should be started in any patient with an AIDS-defining illness (Table 3) and in all HIV-infected patients who are pregnant, have HIV-associated nephropathy, or have hepatitis B virus coinfection when treatment of hepatitis B infection is indicated.

Immunologic reactions have been associated with the initiation of HAART. The most pronounced, immune reconstitution inflammatory syndrome (IRIS), is an inflammatory response to preexisting opportunistic infections that can be observed in 15% to 25% of HIV-infected patients and typically occurs 2 to 12 weeks after starting HAART.⁹ The restoration of pathogen-specific immune responses can lead to eradication or control of opportunistic infections but also leads to immunopathologic conditions in some patients. The protective, but excessive, immune response seen in IRIS is likely a function of inadequate immune regulation and can lead to severe complications, with reported mortality rates as high as 44% to 66% in some patients. Several studies have shown that lower CD4+ T cell counts at the time of HAART initiation and a rapid decline in viral load as a result of

HAART increase the risk of developing IRIS.¹⁰ In addition, the use of the highly potent HIV HAART regimens is an independent risk factor for the development of IRIS. Furthermore, patients who have not initiated treatment for and underlying opportunistic infection present earlier after the initiation of HAART when compared with patients who are already being treated. This suggests that organism burden contributes to the immunopathogenesis of IRIS. Corticosteroids may aid in the treatment of IRIS.¹¹ Additionally, case reports have also suggested that the leukotriene receptor antagonist montelukast may be beneficial.¹²

Hyperimmunoglobulin E

Within 2 years of the initial discovery of HIV in 1981, elevated total IgE levels were reported in HIV-infected patients,⁵ with many investigators subsequently reporting sim-

Table 3. AIDS-Defining Illnesses⁶¹

Bacterial pneumonia (≥2 episodes in 12 months)
Candidiasis of the bronchi, trachea, lungs, or esophagus
Cervical carcinoma, invasive
Coccidiomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1-month duration)
Cytomegalovirus disease (other than liver, spleen, or nodes)
Encephalopathy, HIV-related
Herpes simplex: chronic ulcers (>1-month duration), or bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1-month duration)
Kaposi sarcoma
Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
Lymphoma, Burkitt, immunoblastic, or primary central nervous system
<i>Mycobacterium avium</i> complex (MAC) or <i>Mycobacterium kansasii</i> , disseminated or extrapulmonary
<i>Mycobacterium tuberculosis</i> , pulmonary or extrapulmonary
<i>Mycobacterium</i> , other species or unidentified species, disseminated or extrapulmonary
<i>Pneumocystis jiroveci</i> pneumonia
Progressive multifocal leukoencephalopathy
<i>Salmonella</i> septicemia, recurrent
Toxoplasmosis of the brain
Wasting syndrome due to HIV

ilar findings.¹³ Furthermore, a strong inverse correlation has appeared between IgE levels and CD4+ cell counts. Several studies have demonstrated that an elevated total IgE level in HIV-infected patients is associated with progressive immunodeficiency,^{13,14} and it appears to be a strong indicator of advancing HIV disease. However, increased total IgE levels in HIV-infected patients do not appear to be caused by underlying atopic disease.^{13,15,16} Elevated IgE levels are likely secondary to polyclonal stimulation of B cells or IgE production specific for bacteria, fungi, viruses, and HIV antigens.

Investigators also have suggested that the increased levels of IgE seen in HIV-infected patients might be attributed to a switch from a TH1 to a TH2 cytokine profile during the course of HIV infection. Increased production of interleukin (IL)-4 (the cytokine responsible for IgE class switching) and IL-10 (the cytokine responsible for down-regulation of TH1 cytokines) have been reported in later stages of HIV infection.^{17,18} In addition to promoting IgE production, the increase in TH2 cytokines inhibits the ability of TH1 cells to synthesize IL-2, IL-12, and interferon (IFN)-gamma, as well as antiviral cytotoxic T lymphocyte activity. This may play a critical role in the progression of HIV infection.

Allergic Rhinitis

Patients infected with HIV show an increased prevalence of atopy in the early stages of infection, which tends to decrease as patients progress to AIDS.^{19,20} Allergic rhinitis and sinusitis are frequently seen in HIV-positive patients. In a survey of 203 HIV-positive outpatients, 66% reported sinonasal symptoms.²¹ Another study, using sinus computed tomography, nasal endoscopy, and clinical findings, reported that 35% of hospitalized HIV-positive patients fulfilled the criteria for rhinosinusitis.²² Several authors also have reported an increased prevalence of positive skin prick tests to common aeroallergens when compared with HIV-negative controls.^{20,23} The observation that allergic rhinitis may be increased in patients with HIV infection supports the hypothesis that immune dysregulation caused by HIV impairs normal allergy control mechanisms, leading to increased clinical expression of allergic disease.^{18,24}

Pharmacologic treatment of allergic rhinitis in HIV-positive patients is similar to treatment in HIV-negative patients. Allergen avoidance, oral and intranasal antihistamines, decongestants, and topical steroids can be used without additional precautions.²⁵ Similar to HIV-negative patients, many HIV-positive patients with allergic rhinitis have symptoms that do not respond to avoidance or pharmacologic interventions. Use of allergen immunotherapy (AIT) in HIV-positive patients remains controversial. Theoretical concerns over potential worsening of underlying HIV disease by repeated antigen exposures have been raised with regard to the use of AIT in HIV-infected patients.²⁶ In addition, the effects of T cell modification that occurs during AIT on viral load and CD4+ cell counts are largely unknown. Despite these hypothetical concerns, 40% of allergy-immunology practitioners reported that they would start HIV-positive patients on AIT just as they would

other patients, whereas 9% reported that they would prescribe immunotherapy only for insect venoms.²⁷

No controlled studies have been published evaluating the efficacy or risks associated with AIT in HIV-infected patients. However, several vaccine studies (influenza, yellow fever, pneumococcal) have shown only minimal effects on CD4+ cell counts and viral load.²⁸⁻³⁰ In addition, case reports on the use of AIT in HIV-positive patients receiving HAART have all shown improvement in allergic rhinitis symptoms and no change in CD4+ cell count or long-term viral load, excluding 1 patient who stopped HAART.³¹⁻³³ The 2011 allergen immunotherapy practice parameter states that immunotherapy can be considered in patients with immunodeficiency and proposes guidelines for use of AIT in HIV-infected patients. If the option of using AIT in HIV-infected patients is considered, the potential risks and benefits of AIT in HIV-positive patients must be assessed on an individual basis. Allergen immunotherapy should be limited to unavoidable allergens and should be considered only after avoidance measures and pharmacotherapy options have proved inadequate. Potential AIT candidates also should have no history of opportunistic infections or AIDS-defining illnesses and an undetectable or low viral load. Interval monitoring of CD4+ cell counts and viral load, monthly for the first 3 months and then quarterly, is also recommended.³⁴

Adverse Drug Reactions

Adverse drug reactions have been reported to occur at a much higher frequency in HIV-infected patients. The proposed mechanisms are multifactorial and include immune dysregulation, alterations in drug metabolism, cytokine dysfunction, oxidative stress, and genetic predisposition.³⁵ With the exception of trimethoprim-sulfamethoxazole (TMP-SMX) and abacavir (a nucleotide reverse transcriptase inhibitor), few studies have documented an immune-mediated response as the cause of HIV-associated adverse drug reactions.³⁶ When HIV/AIDS was initially recognized, adverse drug reactions were most frequently related to antimicrobials that were used to treat or prevent HIV-associated infections. With the advent of HAART, these drugs are used less frequently, and adverse reactions are now more commonly associated with antiretroviral therapy itself. Adverse reactions, desensitization protocols, and graded challenges have been reported for most antiretroviral and many commonly used antibiotics, but several warrant individual discussion.

Adverse reactions to TMP-SMX have been well described in HIV-infected patients. Adverse reactions to TMP-SMX occur in 44% to 83% of HIV-infected patients compared with less than 10% of the general population.³⁷ Reactions to TMP-SMX range from an isolated maculopapular or morbilliform rash to severe systemic symptoms and even death. The TMP-SMX hypersensitivity syndrome is an immune-mediated reaction that can occur 7 to 14 days after initiation of the drug. The syndrome includes fever and involvement of 1 or more organ systems. The associated rash can progress to Stevens-Johnson syndrome or toxic epidermal necrolysis. The exact

mechanism of TMP-SMX adverse reactions is not fully understood but likely involves a combination of metabolic and immunologic factors that ultimately culminate in a cytotoxic T cell response.³⁵

Despite their high prevalence, little is known about the optimal management of adverse events caused by TMP-SMX. Treatment is generally supportive and includes withdrawal of the drug. Treating AIDS patients with corticosteroids within 24 hours of starting TMP-SMX has been shown to decrease the incidence of adverse reactions.³⁸ In addition, a meta-analysis of 35 randomized trials reported that the rate of adverse events was decreased by 43% without loss of efficacy if 1 double-strength TMP-SMX tablet was given 3 times per week instead of daily.³⁹ Several desensitization and graded challenge protocols have recently been reviewed for use in patients with TMP-SMX hypersensitivity, with reported success rates ranging from 80% to 100%.³⁵

Abacavir hypersensitivity reaction (ABC HSR) is a multi-organ, potentially life-threatening reaction that occurs in 5% to 8% of HIV-infected patients treated with the nucleoside reverse transcriptase inhibitor abacavir.³⁵ Symptoms usually begin within 9 to 11 days after initiation of therapy and progressively worsen with continued drug exposure. Symptoms are typically associated with a combination of fever, rash, and malaise, in addition to respiratory or gastrointestinal symptoms. Symptoms typically resolve within days of discontinuing abacavir but recur more quickly and severely on rechallenge. Because of the severity of rechallenge reactions, ABC HSR is an absolute contraindication to subsequent treatment with any regimen containing abacavir. Although the exact mechanism of ABC HSR is unknown, an immunologically mediated basis is suspected given the rapid and severe nature of rechallenge reactions. In addition, abacavir patching testing has been successfully used to confirm a clinical diagnosis and to identify true immunologically mediated ABC HSR.⁴⁰ In contrast to TMP-SMX reactions, the risk of ABC HSR has not been shown to be decreased with concomitant corticosteroid administration.⁴¹

Risk factors for ABC HSR have been identified and include white race, a CD8+ cell count greater than 850 cells/ μ L, and most importantly, the presence of HLA-B*5701.⁴² All patch test-positive ABC HSR patients identified worldwide have been HLA-B*5701 positive.⁴⁰ Screening for HLA-B*5701 in populations with an increased prevalence of this haplotype has proved highly effective at identifying patients who are at increased risk for ABC HSR. Screening eliminated immunologically confirmed ABC HSR, with a negative predictive value of 100% and a positive predictive value of 47.9%.⁴³ The overall prevalence of HLA-B*5701 is approximately 8% in whites, 2.5% in African Americans, 2% in US Hispanics, and 1% in US Asians, leading to recent US guidelines recommending that all patients be screened for HLA-B*5701 before starting abacavir and that HLA-B*5701-positive patients avoid any formulation containing abacavir.⁴⁴

The nonnucleoside reverse transcriptase inhibitor nevirapine has also been associated with adverse drug reactions.

The most common manifestation is a nonurticarial rash occurring within the first 6 weeks of therapy. Rashes occur in up to 19% of patients taking nevirapine, with severe life-threatening rashes occurring at a rate of up to 1%.³⁵ Hepatotoxicity also has been described and often is associated with cutaneous reactions and intrahepatic eosinophilic infiltrates, suggesting an immune mechanism. Elevated transaminases are found in 7% of patients, with 1% developing hepatitis.³⁶ Human immunodeficiency virus-negative patients are also at risk for serious reactions to nevirapine; as such the use of nevirapine for postexposure prophylaxis is no longer recommended. Effective guidelines have been published for the prevention, diagnosis, and management of nevirapine-associated reactions.⁴⁵ Absolute avoidance is necessary in patients who develop nevirapine hepatotoxicity or severe life-threatening cutaneous reactions.

Pulmonary Manifestations

Infectious pulmonary complications in patients with HIV have been greatly reduced with the use of HAART and with effective methods of *Pneumocystis jiroveci* prophylaxis. However, immunocompetent, HIV+ patients continue to experience a higher frequency of pulmonary symptoms despite the decrease in infectious complications.⁴⁶ Several observations have suggested that chronic HIV infection may directly or indirectly affect the lower respiratory tract. Human immunodeficiency virus infection has been directly associated with several different noninfectious manifestations of pulmonary disease, including airway hyperreactivity (AHR), asthma, and chronic obstructive pulmonary disease (COPD).

Before HAART, AHR was believed to be no more prevalent in HIV-positive patients than in the general population. The CD4+ lymphopenia seen with advancing HIV disease was thought to be protective against the development of AHR. Indeed, several studies performed before the use of HAART found no increase in the prevalence of AHR in HIV disease.

In contrast, most studies conducted after the introduction of HAART have consistently reported an increased association between smoking, respiratory symptoms, AHR, and asthma in HIV-infected patients receiving HAART. Poirier et al⁴⁷ compared HIV-positive and HIV-negative men and found that HIV-positive men were more likely to report recent wheezing and to demonstrate AHR to methacholine challenge when compared with HIV-negative controls.⁴⁷ In addition, the high prevalence of wheezing and AHR in a cohort of HIV-positive smokers compared with HIV-negative smokers suggests that HIV-positive smokers may be particularly susceptible to the negative effects of cigarette smoke.

Using asthma medications as a marker, Foster et al⁴⁸ subsequently reported an increased incidence of asthma in HIV-positive children receiving HAART compared with HIV-positive children who had not received HAART.⁴⁸ In addition, a recent publication by George et al⁴⁹ has confirmed prior reports that respiratory symptoms remain common in HIV-positive patients and are significantly associated with

smoking. Furthermore, after controlling for other associated risk factors, they reported that the use of HAART was independently associated with a decreased forced expiratory volume in 1 second/forced vital capacity, suggesting a possible direct link between HAART and airway obstruction.⁴⁹ Taken together, these and other similar studies suggest that HIV-positive patients receiving HAART, particularly those who smoke, may be at increased risk for noninfectious respiratory symptoms, AHR, and asthma.

Human immunodeficiency virus infection also has been associated with several different manifestations of COPD, including emphysema. An increased prevalence of emphysema was reported in HIV-positive patients in several studies conducted before the advent of HAART, even in patients who had no history of AIDS-related pulmonary complications. Only 1 study has evaluated the association between HIV infection and COPD in patients receiving HAART.⁵⁰ Comparing HIV-positive with HIV-negative men, the diagnosis of COPD was determined using the International Classification of Diseases, Ninth Revision, diagnostic codes and patient self-report. In both groups, the prevalence of COPD increased according to pack-years of smoking. However, after adjusting for differences in age, smoking, and ethnicity, HIV-positive patients were still 50% to 60% more likely to have COPD compared with HIV-negative controls. The results of this study suggest that HIV infection may be an independent risk factor for COPD.

The exact process by which HIV infection and HAART increase the risk of AHR and COPD is unknown; however, the immune reconstitution achieved with HAART appears to provoke inflammatory responses in some patients.⁴⁹ In animal models, the loss of CD4+ T cells protects against asthma,⁵¹ and in HIV-positive adults, asthma has been associated with higher CD4+ T cell counts.²⁵ It has therefore been proposed that immune reconstituted CD4+ T cells become activated by infectious agents (HIV itself or other organisms colonizing the airways) stimulating the release of inflammatory cytokines that may promote airway inflammation. In addition, CD8+ T cells are believed to play a critical role in the development of COPD. Human immunodeficiency virus infection has been shown to cause an infiltration of CD8+ T cells in the lung.⁵² These cytotoxic T lymphocytes secrete IFN-gamma and have specific activity against HIV-infected cells, especially alveolar macrophages. Although the role this plays in the development of COPD in HIV-positive patients is unclear, overexpression of IFN-gamma has been shown to cause emphysema in animal models. Taken together, these data suggest that immune reconstitution in HIV-infected patients treated with HAART leads to an increased risk of AHR, COPD, and related disorders. Additional studies are needed to further delineate the link between HIV infection, immune reconstitution attributable to HAART, and the development of these pulmonary disorders.

AHR, asthma, and COPD are emerging as important clinical problems in HIV-positive patients in the era of HAART. No studies have addressed the management of these condi-

tions specifically in HIV-positive patients. Given the lack of data, current treatment should follow management guidelines proposed for HIV-negative patients. However, given the risks for oral candidiasis and the increased risk of pneumonia associated with the use of inhaled corticosteroids in patients with COPD, providers should monitor for infectious complications. Likewise, the regular use of systemic corticosteroids should be avoided if possible. In addition, smoking rates are nearly 2 times higher in most HIV-positive compared with HIV-negative populations, and current smoking is associated with increased respiratory symptoms, COPD, bacterial pneumonia, mortality, and decreased quality of life in HIV-positive patients.⁵³ Providers therefore should make smoking cessation a top management priority.

Food Allergy

Although allergic rhinitis, adverse drug reactions, AHR, and COPD are more common in HIV-positive patients, current evidence suggests that the prevalence of food allergies is not increased compared with the general population. The estimated prevalence of food allergy in the general population ranges from less than 3% in adults up to 6% to 8% in children.⁵⁴ Only 1 study has evaluated the prevalence of food allergies in HIV-positive patients. Tubiolo et al⁵⁵ evaluated a cohort of HIV-positive patients and reported a food allergy prevalence of 0.57% (confirmed by double-blind, placebo-controlled food challenge) to 5.7% (based on history alone). Although HIV-infected patients have risk factors for food allergies including increased IgE production, an increase in other atopic disorders, and altered gastrointestinal mucosal function caused by infection, they do not appear to be at increased risk for food allergies.

Routine Immunization

Allergy-immunology practitioners may be consulted regarding vaccination of HIV-positive patients. Human immunodeficiency virus infection is a risk factor for increased morbidity and mortality caused by a number of vaccine-preventable infections. Because antigen stimulation leads to activation of CD4+ T lymphocytes and subsequent increased HIV replication, concerns have been raised that immunization might increase viral production and the depletion of CD4+ T cells. Since the mid-1990s, much has been published regarding the safety and efficacy of vaccines in the setting of HIV infection. Although some vaccines may induce temporary increases in HIV replication, no evidence has been found indicating that this is of any clinical significance.

In general, inactivated vaccines can be administered safely to persons with HIV infection and should be given at the usual doses and recommended schedules (Table 4).⁵⁶ Although the effectiveness of such vaccines might be suboptimal and can decrease with advancing disease, improved responses can be achieved when vaccines are given early in the course of HIV infection. Vaccines specifically targeting HIV are also actively being investigated but are outside the scope of this review.

Table 4. Routine Immunization Schedule for Adults Infected with HIV⁶²

Vaccine	Recommendation
Inactivated influenza	1 Dose annually
Pneumococcal (polysaccharide)	1 Initial dose and 1 booster 5 years later
Hepatitis B	3 Doses
Tetanus, diphtheria, pertussis	Substitute 1-time dose of Tdap for Td; then boost with Td every 10 years
Human papillomavirus	When the clinician believes clinical benefit can be derived
Measles, mumps, rubella (MMR)	Do not administer to severely immunocompromised persons
Varicella	Do not administer to severely immunocompromised persons
Hepatitis A	2 Doses

The incidence of secondary infections in HIV-positive patients has decreased since the introduction of HAART. However, invasive pneumococcal disease continues to be substantially higher among HIV-infected patients compared with HIV-negative controls.⁵⁷ Although antibody responses to the 23-valent pneumococcal polysaccharide vaccine (PPV) are generally lower in HIV-positive patients than in healthy controls, vaccination with PPV has been shown to significantly reduce the risk of pneumonia among HIV-infected patients.⁵⁸ Current guidelines recommend giving PPV to adults and children 2 years old or older with CD4+ counts greater than 200 cells/ μ L as soon as HIV is diagnosed (unless received during the previous 5 years).⁵⁹ In addition, because the duration of protection is unclear, a single booster dose after an interval of 5 years is also recommended.

Persons with severe cell-mediated immune deficiency are generally not given live attenuated vaccines. However, HIV-infected children are at increased risk for severe complications of varicella, herpes zoster, and measles. Varicella vaccine has been shown to be safe and effective in HIV-infected children and is recommended for children 8 years old or younger with a CD4+ T cell count of at least 200 cells/ μ L and at least 15% of the total T cell population.⁶⁰ No studies have evaluated the varicella vaccine in HIV-infected adolescents or adults; however, varicella vaccination (2 doses, administered 3 months apart) may be considered in HIV-positive/varicella nonimmune persons older than 8 years old with CD4+ counts of at least 200 cells/ μ L.⁵⁹ Given a lack of data, use of the herpes zoster vaccine in HIV-infected patients is currently not recommended.

Current guidelines also recommend using the mumps-measles-rubella vaccine in age-appropriate HIV-infected patients with a CD4+ T cell count of at least 200 cells/ μ L. No safety or efficacy data evaluating the use of rotavirus vaccine in HIV-infected infants are available. The decision to use the rotavirus vaccine in HIV-exposed or infected infants should take into account the potential risks and

benefits and should be individualized to each specific patient. The live-attenuated influenza vaccine should not be given to HIV-infected patients. They should instead receive the inactivated influenza vaccine annually during influenza season.⁵⁹

Human immunodeficiency virus-infected patients also may have indications to receive nonroutine immunizations. Patients at risk for exposure to typhoid fever should be given the inactivated parenteral typhoid vaccine instead of the live-attenuated oral preparation. Limited safety and efficacy data are available regarding the use of the yellow fever vaccine in HIV-infected patients. A recent study evaluating its safety and efficacy reported no adverse events and protective titers in HIV-infected patients with CD4+ cell counts of at least 350 cells/ μ L.³⁰ Travelers with asymptomatic HIV infection who cannot avoid potential exposure to yellow fever should be offered vaccination.⁵⁹

CONCLUSION

Allergic diseases are common in HIV-infected patients. With the use of HAART and the subsequent decrease in infectious complications, HIV-infected patients now live longer and experience common chronic diseases. Allergic rhinitis, asthma, and adverse drug reactions are conditions for which allergy-immunology practitioners are frequently consulted. Evaluation of HIV-infected patients with these conditions may become more frequent as HAART continues to extend the life expectancy of patients living with HIV. Knowledge of the impact of HIV on the immune system and on therapies used to treat allergic conditions can help practitioners effectively and safely provide care for HIV-infected patients.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

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CME Examination

1–5, Stokes SC. 2011;107:1–9.

CME Test Questions

1. Elevated IgE levels in HIV-infected patients have been shown to correlate with
 - a. An increased prevalence of atopic conditions
 - b. Improved immune function
 - c. Progressive immune dysfunction
 - d. Parasitic infection
 - e. A shift toward increased levels of TH1 cytokines
2. Risk factors for the development of immune reconstitution inflammatory syndrome include all of the following *except*
 - a. A low CD4+ T cell count when highly active anti-retroviral therapy (HAART) is initiated
 - b. A high CD4+ T cell count when HAART is initiated
 - c. A rapid decline in viral load as a result of HAART
 - d. The use of highly potent HAART regimens
 - e. Untreated opportunistic infections before HAART initiation
3. Which of the following confers the greatest risk of developing abacavir hypersensitivity reaction?
 - a. Being of African-American descent
 - b. Having a very low CD8+ T cell count
 - c. Carrying the HLA-B*27 allele
 - d. Carrying the HLA-B*5701 allele
 - e. Carrying the HLA-DQB1 allele

4. Which of the following statements regarding HIV-infected patients is true?
 - a. Patients receiving HAART have a decreased prevalence of airway hyperreactivity and asthma
 - b. Patients receiving HAART are at increased risk for developing chronic obstructive pulmonary disease
 - c. HIV-infected patients have an increased risk of developing food allergies
 - d. All of the above
 - e. None of the above
5. All of the following statements regarding immunization of HIV-infected patients is true *except*
 - a. Inactivated vaccines can be safely given to HIV-infected patients
 - b. Asymptomatic HIV-infected patients $\geq$ 2 years old should receive the pneumococcal polysaccharide vaccine
 - c. The live-attenuated varicella and mumps-measles-rubella vaccines should not be given to asymptomatic HIV-infected children
 - d. The live-attenuated influenza vaccine should not be given to HIV-infected patients
 - e. HIV-infected patients at risk for exposure to typhoid fever can receive the inactivated parenteral typhoid vaccine