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Preface

The AIDS epidemic, which began in the early 1980s, is still ongoing and has touched all aspects of our society. The study of this retroviral infection has greatly expanded our knowledge of the immune system and infections. The earliest observations from patients infected with the AIDS virus had a decrease in their $CD4^+$ lymphocyte, which led investigators to start to unravel the role that the $CD4^+$ lymphocyte plays in the activation of the immune system and how the loss of this T-cell regulation affects B-lymphocyte function.

Later in the study of the AIDS virus, the macrophage, an antigen-presenting cell to the $CD4^+$ lymphocyte, was found to be a reservoir for the AIDS virus, which furthered our understanding of the critical functions of the macrophage in immune recognition in health and disease. The lessons that we have learned about the immune system are still forthcoming, yet we are already applying the knowledge to the clinical care of the HIV patient.

Alterations in the immune system that result from the HIV infection present the clinician with many challenges. These patients develop rheumatic diseases including vasculitis, arthritis, and myositis. The alterations in the immune system can also predispose these patients to drug hypersensitivities and allergic reactions.

Today, the care of the HIV-infected patient is challenging. In *AIDS Allergy and Rheumatology* we present the clinician with the most current and practical information regarding the rheumatic and allergic issues that they will regularly be facing while providing medical care for an HIV-infected patient.

Nancy E. Lane

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AIDS Allergy and Rheumatology

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Introduction

The AIDS epidemic, which began in the early 1980s, is still ongoing and has touched all aspects of our society. The study of this retroviral infection has significantly expanded our understanding of the immune system. The early observation that patients infected with the AIDS showed a decrease in the number of their $CD4^+$ lymphocytes led investigators to unravel the role that the $CD4^+$ lymphocyte plays in the activation of the immune response and how the loss of T-cell regulation affects B-lymphocyte function. Later, the observation that the macrophage—an antigen-presenting cell to the $CD4^+$ lymphocyte—was a reservoir for the AIDS virus furthered our understanding of critical functions of the macrophage in immune recognition in health and disease. The lessons we have learned about the immune system are still forthcoming.

In the first chapter of *AIDS Allergy and Rheumatology*, Michael McGrath reviews the immunologic changes that occur in the major targets for HIV-1 infection, the T-cell, and the macrophage. The second chapter by Valerie Ng reviews the in vitro and in vivo effects of HIV-1 infection on B-cells.

After a review of the immunologic defects that result from HIV-1 infection, we focus our attention on the clinical manifestations of this infection. Rheumatic complications can occur at any time during the course of HIV disease and diseases, such as Reiter's syndrome, psoriatic arthritis, polymyositis, and necrotizing vasculitis, may sometimes be the first clinical clue to the presence of the HIV infection. Brian Kaye has extensively reviewed the rheumatic manifestations of HIV infec-

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tions, focusing on arthritis, myopathies, vasculitis, sicca syndrome, and other autoimmune phenomena. The rheumatic diseases that HIV-infected individuals develop can severely impair their quality of life and the drugs, such as methotrexate, that are commonly used to treat rheumatologic conditions may in fact hasten the development of opportunistic infection in these individuals. The chapter also gives appropriate treatment guidelines.

Dermatologic manifestations of HIV disease, whether infectious or immunologic in origin, need to be diagnosed and treated rapidly in HIV-infected individuals to prevent further complications. A comprehensive review of psoriasis associated with HIV infection is provided by Timothy Badger, Timothy Berger, Charles Gambla, and John Koo. The clinician is provided with practical advice for the diagnoses and treatment of this disease.

Another clinical manifestation of immune dysregulation that occurs with HIV infection is hypersensitivity and allergic reactions. Drug hypersensitivity remains the most frequent untoward reaction, but chronic nasal symptoms and pruritic cutaneous disorders are also commonly observed allergic manifestations of HIV infection. Drs. Avila and Kishiyama extensively review the proposed pathophysiological mechanisms, diagnosis, and management of different clinical allergic disorders affecting HIV patients, and discuss controversial issues regarding immunotherapy in HIV disease. In the last chapter, Belle Lee reviews one of the most common drug hypersensitivities encountered in the HIV-infection population, adverse reactions to trimethoprim-sulfamethoxazole.

I thank all of the authors for their willingness to share their knowledge of the rheumatic and allergic manifestations of AIDS, and Eric Gershwin, the editor of the *Allergy and Immunology: Clinical and Experimental Progress* series for developing this volume for clinicians.

The past 15 years have seen a tremendous increase in our understanding of the impact of the HIV infection on the immune system, and as clinicians, we are able to treat the manifestations of this disease. I look forward to the next few years when we have the therapies both to prevent and cure this disease.

T-Cells and Macrophages in HIV Disease

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Introduction

HIV infection in humans is associated with a broad spectrum of immunologic abnormalities *(1)*. This brief article focuses on immunological changes that occur in the major targets for HIV infection, the T-cell, and the macrophage.

T-Cells

T-cells are thymus-derived lymphocytes that can be broadly subdivided into two major classes based on cell-surface antigen expression. These are the CD4 and CD8 subsets. In normal blood, the CD4 to CD8 ratio is approx 2:1. The CD4 cell subset functions both to help (T-helper) B-cells differentiate and secrete antibody reactive against specific antigens, and to induce cellular immunity, which involves induction and activation of CD8-expressing T-cells. This inducer CD4 cell is also the source of the T-cell growth factor, interleukin-2 (IL-2). These helper and inducer subclasses of T-cells have further been named by the cytokines they make on activation. The inducer subclass, or T_H-1, class of lymphocyte when stimulated makes interferon-γ and IL-2. The helper subpopulation of CD4 cells, or T_H-2 cells, on activation express, IL-4, 5, 6, and 10 *(2–4)*. Both of the CD4 subclasses of the cell differentiate from an earlier T_H-0 cell that makes IL-4 and interferon-γ when stimulated. A final CD4-expressing cell population, which requires induction by the aforementioned CD4 cell, is the delayed-type hypersensitivity T-cell involved in fighting mycobacterial infection.

The principal role of the CD8 cell population is the killing of virus-infected cells, cancers, or cell-associated invading organisms. These

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cells are the CD8 cytotoxic T-lymphocytes. The other CD8 subset of cells is represented by the T-suppressor cell population, which is still poorly defined.

Approximately 1–2% of the body's lymphocytes are present in the blood at any given point in time. On induction of a new immune response in association with a serious viral infection, the CD4 population of cells migrates to lymphoid organs to begin initiation of immune responses. The CD4 cells become activated after interacting with an antigen-presenting cell, the most potent of which are the dendritic and follicular dendritic cells. Further immunologic responses, such as activation of antibody production, and activation of cytotoxic T-lymphocytes then ensue.

T-Cells and HIV Disease

On initial infection with HIV, there is a drop in circulating CD4 cell number, which rebounds somewhat after an individual develops immunity to HIV. There is an associated rise in circulating CD8 cells, which gives rise to an inverted ratio of CD4 to CD8 cells in the peripheral blood *(5)*. The progression in an infected individual to symptomatic HIV disease occurs after the CD4 cell number goes below 200 CD4 cells/μL with an average loss of CD4 cells of approx 60/μL/yr after infection *(6)*. In severe HIV disease, CD4 cell numbers can fall so low as to be virtually undetectable. The rate of CD4 cell fall is variable, but can be broadly defined into three categories *(7)*.

Individuals who progress rapidly from HIV infection to symptomatic AIDS, typically within 2–3 yr of infection, have a very rapid fall in their CD4 cell number. This patient population represents approx 10% of infected individuals. On the other end of the spectrum are individuals whose CD4 T-cells remain stable at over 500/μL. These represent long-term, nonprogressors and also make up around 10% of the HIV-infected population. The typical HIV-infected patient has a gradual loss of CD4 cells over a 10-yr period that shows a marked decline beginning around 18–24 mo prior to an AIDS-defining diagnosis. Over the course of HIV infection, there is a switch from a T_H-1 to T_H-2 CD4 cell genotype *(8)*. In other words, there are fewer cells capable of making IL-2 (T_H-1 CD4 cells), which serve to expand cellular immunity, than cells of the T_H-2 type, which cause B-cell proliferation, differentiation, and antibody secretion. Clinically, the patient shifts from being able to fight off chronic viral infections and cancers, which require T_H-1-type responses to developing hypergammaglobulinemia, which is a characteristic of a type 2 response in later stage HIV disease.

CD8 Cells in HIV Disease

CD8 T-cell numbers increase over the early course of HIV infection and have at least two forms of anti-HIV activities. At approx 2–4 wk after infection, CD8 cells reacting with HIV-infected cells appear *(9–11)*. These are major histocompatibility class (MHC) 1-restricted CD8-expressing cytotoxic T-lymphocytes (CTL). The CTL response against HIV is the first immunologic response, is responsible for causing a fall in viral load seen at 2–4 wk after infection, and occurs prior to seroconversion. Another class of CD8 cells also appears early in HIV disease that is not directly cytotoxic for HIV-expressing cells, but appears to produce antiviral factors *(12,13)*. This CD8 cell population expresses factors that inhibit HIV expression in CD4 cells. Unlike the CTLs, this CD8 population is not MHC-restricted in its anti-HIV activity. Long-term nonprogressor patients have high levels of this activity, which persists for years *(7)*. Patients who progress rapidly quickly lose this CD8 cell population. Patients with a typical course of HIV disease begin losing this CD8 cell population around 2 yr prior to the development of symptomatic AIDS. The loss of this CD8 population is associated with a precipitous fall in CD4 numbers, suggesting that this CD8 cell may be important for keeping HIV under control in vivo. Recently three chemokines have been identified as having anti-HIV activity after production by CD8 cells. These were RANTES, MIP-1α, and MIP-1β *(14)*. Whether these are the only anti-HIV cytokines to be produced by CD8 cells remains to be determined.

Mechanism of CD4 Cell Loss

Over time after HIV infection, the CD4 cell number goes from normal ranges (600–1400/μL) to very low numbers as described earlier. Recent evidence on virus replication kinetics suggests that over 10^9 CD4 cells are lost per day and that that cell loss is through virus replication with subsequent CD4 cell death *(15,16)*. Therefore, it is likely that the major reason for CD4 cell loss in vivo is from direct cytopathic effects of virus replication on the CD4 cell.

Another mechanism for CD4 cell loss is through inappropriately high levels of CD4 cell-programmed cell death or apoptosis *(17,18)*. A number of studies, have shown that when peripheral blood mononuclear cells from HIV-infected patients are placed in vitro, an elevated rate of apoptosis occurs. Normally, lymphocytes from a non-HIV-infected individual would undergo apoptosis at a <3% rate over a 3-d period of culture. In contrast, up to 35% of lymphocytes from HIV-infected patients undergo spontaneous apoptosis when cultured in vitro. Whether this high rate of apoptosis occurs in vivo is still uncertain.

One of the earliest studies on mechanisms by which CD4 T-cells might be lost in vivo is through a mechanism called syncytium formation *(19)*. It is known that after HIV binds to cell-surface CD4, it fuses with the cell membrane and empties its RNA genome into the infected cell. This interaction is mediated through HIV envelope glycoprotein gp120/gp41 interacting with the CD4 molecule *(20,21)*. On a more macroscopic level, HIV-infected cells that come into contact with CD4-expressing uninfected cells will similarly fuse and form multinucleated giant cells. This is a common observation in in vitro culture systems, and multinucleated giant cells have been observed to occur in vivo mostly in brains of patients with AIDS-associated dementia *(22)*.

The immune response against HIV may also be harmful for CD4 cells. For example, gp120, which interacts with the cell-surface CD4 molecule, may allow the immune system to recognize uninfected gp120-complexed CD4 cells as foreign. This would allow natural killer cells to identify antibodies bound to gp120 in association with the CD4 cell and kill it through an antibody-dependent cellular cytotoxicity (ADCC) mechanism *(23)*. The CD8 anti-HIV CTL may also kill CD4 cells with adsorbed gp120 *(24)*. Therefore, anti-HIV CTL may be good in certain circumstances and harmful in others.

Although a fall in the CD4 cell population is the hallmark of HIV disease, the CD8 cells also fall late in HIV disease *(5,7,25)*. The fall begins somewhere between 18 and 24 mo prior to symptomatic AIDS. It is unlikely that CD8 numbers decrease secondary to direct viral replication. However, with the gradual loss of the inducer CD4 cell, the producer of IL-2, the entire immune system would lose the capability of expanding T-cell populations. As described earlier, apoptosis is observed in HIV-infected patient lymphocytes, and this process does not discriminate between CD4 and CD8 cells, since both subsets of cells are observed to undergo apoptosis at an elevated rate. Therefore, CD8 cell loss may be a product both of apoptosis and loss of the immune system's ability to generate IL-2 for further CD8 cell expansion.

Monocytes and Macrophages

Monocytes circulate in the blood for approx 3 d after release from the bone marrow. They then migrate to tissues and become tissue macrophages. The Kupfer cells in the liver are apparently the shortest lived macrophage, being replaced every 1–2 mo. The longest lived macrophages could theoretically live as long as a tattoo, which represents a collection of skin macrophages that have phagocytosed colored oil droplets. Macrophages take up foreign substances that enter the body and are absolutely required for T-cell-dependent immunity *(26)*. Macrophages are critical for antigen processing and phagocytosis of par-

ticular foreign invaders of the human body. Through Fc receptor-mediated endocytosis, macrophages efficiently take up organisms that have antibody attached to them.

Macrophages in HIV Diseases

Macrophages express the cell-surface marker CD4, which also is a receptor for HIV *(27)*. Macrophages have been shown to be infectable in vitro through the CD4 receptor as well as the Fc receptor with antibody-coated viruses *(28)*. Unlike T-cells that die when HIV replicates, macrophages can be infected and live for long periods of time in vitro *(27)*. Macrophages are very likely the first cell in the body to be infected by HIV. This is because when strains of HIV from patients with early disease were tested, they were almost always macrophagetropic. It is only later in the disease when one sees a more precipitous T-cell loss that a T-cell tropic strain of virus appears *(7)*.

Functional Characteristics of HIV Disease Associated Macrophages

The majority of blood monocytes in an HIV-infected patient are not infected with HIV. However, there is abnormal function of this cell population. There is a decreased ability to phagocytose yeast in vitro *(29)*. In part, there is an overall dysfunction in phagocytosis ability since virtually all HIV-infected patients have circulating immune complexes that are inefficiently cleared by the body's phagocytic cell system. It is not surprising then that, when tested in vitro, monocytes show a decreased ability to take up foreign substances. This is likely owing to an Fc receptor blockade with excess immune complexes. These abnormalities also contribute to abnormal antigen presentation, a characteristic that contributes to HIV-associated immunodeficiency *(30)*. There is also a decreased response to chemoattractants *(31,32)* and a disruption of normal cytokine expression *(33)*, including the production of an inhibitor of IL-1 capable of blocking the induction of an immune response *(34)*.

Disease Associated with HIV-Infected Macrophages

The major disease associated with infected macrophages is AIDS dementia complex *(35)*. This is a progressive dementia that affects 15–20% of HIV-infected patients in the United States. It is a disease in end-stage AIDS, and patients typically have fewer than 50 CD4 cells when the AIDS dementia process is noticed. Histologically, brains of patients with AIDS dementia are characterized by astrocytosis, multinucleated giant cell formation, microglial nodule formation, and loss of neurons. A prominent feature of this process is the presence of HIV-infected and

HIV-expressing macrophages *(36–38)*. These macrophages are initially noted as being associated with brain capillary endothelial cells and in later disease in the brain parenchyma, and are activated and express HIV as well as TNF-α and IL-1β. TNF-α, normally expressed in activated macrophages, is also associated with causing apoptosis in neuron cultures in vitro. At this time, it is unknown whether macrophages continuously arrive in the brain through the blood–brain barrier, or whether free virus gets into the brain and inflects resident macrophages and microglial cells. In various experimental systems *(39)*, infected macrophages have been found to make substances toxic for human brain cells, including the aforementioned TNF-α as well as gp120, arachidonic acid metabolites, platelet-activating factor, and uncharacterized neurotoxic substances *(40)*.

Another disease that is associated with HIV-infected macrophages is AIDS-associated large-cell lymphoma. In a subset of large cell lymphomas, IL-6 and HIV p24 coexpressing macrophages can be found *(41–44)*. The overproduction of IL-6 appears initially to drive polyclonal lymphocyte proliferation, which can subsequently lead to the emergence of a monoclonal tumor.

In recent studies, a subset of lymphomas had clonal HIV identified using a technique termed "inverse polymerize chain reaction" (IPCR) *(45)*. The clonal form of HIV was localized to tumor-associated macrophages *(46)*. These mixed immunophenotype lymphomas were of large-cell morphology, and the clonal macrophages expressed both HIV p24 and IL-6. This observation suggested a new model of lymphomagenesis wherein early stages would be driven by a clonally expanded macrophage population, making growth factors for a polyclonal population of lymphocytes. In parallel studies, a clonal form of HIV was also found in association with early stages of Kaposi's sarcoma *(47)*. In this case, the macrophages that expressed HIV also coexpressed basic fibroblast growth factor, IL-6, and HIV tat. The aforementioned growth factors are all known stimulators of spindle-cell proliferation, the malignant cell associated with Kaposi's sarcoma. Recently, a broad spectrum of tumors were found to have clonal HIV, including mycosis, fungoides, syncytial Hodgkin's disease, cutaneous anaplastic lymphoma, and angioimmunoblastic lymphadenopathy with dysproteinemia (AILD). In each case, anti-HIV immunostaining localized HIV to the tumor-associated macrophages *(48)*. In these studies where a clonal form of HIV was found in macrophages, a new form of tumorigenesis, termed "sequential neoplasia," was suggested. In this model, HIV integration in a macrophage would cause neoplastic proliferation of that macrophage to occur. In the case of lymphomas, a common integration region was identified just upstream from the c-*fes* oncogene *(45)*. The sequential neoplasia model predicts that depending on where the HIV

is integrated within a macrophage population, an individual will be at risk to develop secondary neoplasia driven by growth factors elaborated by the clonal macrophage. Further studies will be required to determine whether this sequential neoplasia model can be generalized to other disease processes that occur in HIV-infected individuals. Because macrophages do not die after infection with HIV, they are an obvious at-risk cell population for immortization by HIV integration.

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B-Lymphocytes and Autoantibody Profiles in HIV Disease

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Introduction

The normal function of the human immune system and subsequent immunologic protection of the host for external antigenic challenge (e.g., infection) is dependent on the intricate localized interactions of T-cells, B-cells, and macrophages. Infection with the human immunodeficiency virus, type 1 (HIV-1) causes widespread damage to the host immune system, resulting in defective antigen presentation by follicular dendritic cells, loss of T-cell regulation of B-cell function in the presence of chronic antigenic stimulation, destruction of the normal architecture of lymphatic tissue, and disruption of normal cellular networks *(1–3)*. This article focuses on the in vitro and in vivo effects of HIV-1-infection on B-cells.

Normal B-Cell Development and Immunoglobulin (Ig) Production

B-cells, by virtue of antibody or Ig production, form the humoral arm of the immune system. B-cells circulate and comprise approx 3% of peripheral lymphocytes, but the majority of B-cells reside in the bone marrow.

There are two main phases in B-cell development—one antigen-independent (i.e., pre-B cell to mature B-cell), and one antigen-dependent (i.e., B-cell to plasma cell) *(4)*. The first phase is characterized by expression of Ig chains in the cytoplasm exclusively (cytoplasmic μ chains), and the second phase by expression of Igs on the cell surface (i.e., immature, mature, activated, and memory B-cells with cell-surface IgM, IgD, IgG, IgA, or IgE). For H chains, IgM is the first Ig expressed by B-cells responding to a new antigenic challenge, followed by a brief

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period where IgM and IgD are coexpressed on the cell surface, before the B-cell ultimately commits to IgG, IgE, or IgA expression. For L chains, κ chains rearrange before λ chains.

Igs are composed of two heavy (H) and two light (L) chains. Synthesis of H and L chains results from a discrete and coordinated sequence of molecular events. For H chains, specific variable (V_H), diversity (D_H), and joining (J_H) DNA segments are rearranged to form a continuous V_H gene, with intervening DNA between the joined V, D, and J genes excised and excluded from the host genome. For κ or λ L chains, rearrangement of Vκ and Jκ or Vλ and Jλ segments occurs in a similar manner (there is no D segment for L chains). Additional rearrangements to juxtapose different constant regions of the H (to produce IgM, IgD, IgG, IgA, or IgE) or L chains (to produce κ or λ) then occurs with the ultimate production of a functional Ig. V, D, and J segments for H chains are located on chromosome 14, whereas V and J segments for L chains are located on chromosomes 2 (for κ chains) or 22 (for λ chains).

The first level of the Ig repertoire, or diversity of antibodies that could be made by a single individual, is encoded by the large number of potential VDJ combinations possible for H and L chains (there are at least 50 functional V_H genes, 12 D_H genes, 6 J_H genes, 32 functional V_κ genes, 5 J_κ genes, 45 functional V_λ, and 4 functional J_λ genes) *(5–10)*. Additional diversity, over and above all possible recombination events between the multitude of germline genes, is generated by the action of the enzyme terminal nucleotidyl transferase (TdT) that functions during the recombination events to add a variable number of nucleotides ("N" additions) to the V/D/J or V/J junctions, introducing amino acid differences, and thereby modifying the binding site of the antibody V gene. (The "VDJ" or "VJ" segment of an H or L chain, respectively, can thus serve as a "molecular fingerprint" of a specific clone of B-cells, since it is highly unlikely that the same combination of V, D, J genes, and specific N additions/deletions would have occurred in multiple Igs by random chance alone.)

The V regions of both the H and L chains in the intact Ig molecule interact to form a three-dimensional pocket (i.e., idiotope) that binds the cognate antigen. Antigens are recognized on the basis of shape. This shape is ultimately encoded by the primary amino acid sequence of the antigen, but may be comprised of a linear stretch of amino acids or of noncontiguous amino acids brought into juxtaposition by steric forces or disulfide bonding. Thus, a single antibody could bind antigens with different amino acid sequences, but the same shape.

B-cells expressing Igs that best "fit" the cognate antigen will be continuously stimulated to clonally proliferate and can further modify the expressed antibody by a process known as "somatic hypermu-

tation" *(11)*. This process results in nucleotide substitutions occurring in discrete portions of the V gene that form the pocket of the antigen binding site (i.e., the first and second complementarity determining regions). Additional antigen exposure will select for those B-cell clones expressing somatically hypermutated Igs that have a higher affinity and avidity for the inciting antigen.

There is increasing recognition that specific germline V_H genes are preferentially used, and that some of these germline V_H genes encode polyreactive low-affinity antibodies (e.g., VH4.21, VH26; *12–18*). Igs using these V_H genes encoding polyreactive antibodies may explain at a molecular level the polyreactivity observed for IgMs obtained during the early phase of an immune response in normal individuals. In contrast, many of the autoantibodies from patients with autoimmune diseases are often IgGs, exhibit high-affinity for their cognate autoantigen, and have significant numbers of nucleotide changes in their V_H genes occurring in a pattern consistent with that expected for somatic hypermutation, suggesting autoantigen-selection of high-affinity and high-avidity autoantibodies. Current clinical laboratory assays to detect autoantibodies do not discriminate well between antibodies of low or high affinity and avidity, and thus cannot discriminate well between naturally occurring vs pathogenic autoantibodies.

In Vitro Effects of HIV-1 on B-Cells

Direct Infection

B-cells, by virtue of cell-surface expression of the HIV-1 receptor, CD4, can be directly infected with HIV-1 in vitro *(19)*. The significance of this, however, is unclear, since HIV-1-infected B-cells cannot be detected in the peripheral blood of HIV-1-infected individuals.

Functional Abnormalities of B-Cells in HIV-1-Infected Individuals

A variety of in vitro abnormalities can be demonstrated for the circulating B-cells of HIV-1-infected individuals. An observation made early on in the HIV-1 epidemic was that peripheral blood mononuclear cells (PBMCs) of patients with the acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC), when compared to those from healthy homosexual or heterosexual men, had a blunted proliferation response to either T-cell-dependent (e.g., pokeweed mitogen [PWM]) or T-cell-independent polyclonal B-cell mitogens (i.e., *Staphylococcus aureus* Cowan 1 strain [SAC], and Epstein-Barr virus [EBV]) *(20,21)*. The fewer numbers of T-cells in the PBMCs of AIDS or ARC patients did not account for the blunted response to T-cell-dependent B-cell mitogens, and the blunted response to SAC in the presence or

absence of T-cells eliminated the possibility of an increased T-cell suppressor effect on B-cell proliferation in response to T-cell-independent B-cell mitogens.

B-cells from HIV-1-infected individuals spontaneously secreted Igs in vitro, with B-cells from AIDS patients secreting approx 10-fold more than B-cells from healthy homosexual males *(20–23)*. In contrast, Ig secretion could not be induced in B-cells from AIDS or ARC patients with T-cell-dependent polyclonal B-cell mitogens (PWM or concanavalin A) or coculture with allogeneic T-cells *(20,21)*. Although a qualitative defect in T-"helper" function in ARC and AIDS patients was demonstrated, lack of Ig secretion following allogeneic coculture suggested an intrinsic defect in B-cells from HIV-1-infected individuals *(20,21)*.

Despite similar absolute numbers of circulating B-cells in the peripheral blood of normal healthy individuals and AIDS/ARC patients, a higher frequency of spontaneous B-cell outgrowth was noted for those obtained from the peripheral blood of AIDS/ARC patients *(22,23)*. Clonal outgrowths of all spontaneous transformants were infected with EBV, but not with HIV, demonstrating an abnormally high level of circulating EBV-infected B-cells *(22)*. T-cell suppression of Ig secretion by autologous EBV-infected B-cells, as would be expected from non-HIV-infected EBV-seropositive individuals, was absent *(22)*. Defective T-cell regulation of EBV-infected B-cells was postulated to contribute to the increased numbers of circulating EBV-infected B-cells in vivo *(22)*.

A subset of the Igs spontaneously secreted in in vitro culture of B-cells obtained from AIDS or ARC patients was directed against HIV *(23)*. Precursor frequencies for anti-HIV-Ab-producing B-cells were higher in AIDS and ARC patients (compared to normal healthy HIV-seronegative controls) and were not influenced by the presence of PWM or EBV. Levels of secreted anti-HIV-Abs were similarly not affected by the presence of PWM or EBV, but were dependent on the presence of autologous T-cells *(23)*. Of note, normal PBMCs from HIV-seronegative controls secreted Igs in response to purified HIV; a scientific explanation for this unexpected observation was not obvious until it was demonstrated that the HIV-1 envelope glycoprotein, gp120, served as a natural ligand and functionally activated B-cells expressing the D12 surface idiotope *(24,25)*.

In summary, the B-cell abnormalities observed in vitro are consistent with those expected for a hyperactive B-cell state in vivo. Mechanisms postulated to account for this apparent in vivo B-cell activation include chronic antigenic stimulation with ubiquitous viruses (e.g., EBV, HIV, cytomegalovirus [CMV]) in combination with defective T-cell regulation. The inability to induce additional Ig secretion in the presence of PWM or SAC in vitro furthermore suggested that B-cells are maximally activated in vivo.

In Vivo Manifestations of B-cell Dysfunction in HIV-1-Infected Individuals

Hypergammaglobulinemia and Paraproteinemia

Hypergammaglobulinemia is an early manifestation of HIV-1 infection *(26,27)*. A significant proportion (i.e., 9–45%) of HIV-1-infected individuals with hypergammaglobulinemia also had paraproteins superimposed on their polyclonal γ-globulin fractions. Microscopic examination of bone marrows obtained from HIV-1-infected individuals uniformly revealed plasmacytosis *(28)* in the absence of other clinical features of multiple myeloma (i.e., hypercalcemia, lytic bone lesions). Neither the hypergammaglobulinemia, paraproteinemia, nor the increased number of plasma cells in the bone marrow was associated with or predictive of the development of multiple myeloma or any other HIV-1-associated disease *(29,30)*. It has been suggested that the hypergammaglobulinemia observed in vivo may be the in vivo counterpart of the in vitro observation of spontaneous Ig secretion by B-cells obtained from HIV-1-infected individuals.

Purified HIV-1-associated paraproteins contained high-titer anti-HIV antibody titers directed against "gag" and "pol" gene products, suggesting that chronic HIV-1 antigenic stimulation may be driving the production of these paraproteins *(31,32)*. If so, presence of paraproteins might in fact represent an exuberant but normal B-cell response to antigenic challenge in an HIV-1-infected individual. This interpretation might account for the lack of clinical significance of HIV-1-associated paraproteins *(29,30)*. Given the high prevalence of non-Hodgkin's B-cell lymphoma in the HIV-1-infected population, it has been hypothesized that continuous HIV-1 antigenic stimulation of anti-HIV-1 paraprotein producing B-cell clones would provide a population of rapidly proliferating B-cells susceptible to additional genetic events that could lead to outgrowth of a transformed clone and clinical manifestation as lymphoma. In support of this hypothesis, there has been a single report of a high-titer anti-p24 paraprotein in an HIV-1-infected individual who had a monoclonal B-cell population in his bone marrow, but definitive proof that the paraprotein was produced by the monoclonal B-cells was lacking *(33)*. In opposition to this hypothesis, development of a B-cell lymphoma coincided with disappearance of an anti-HIV-1 paraprotein, suggesting that the lymphoma did not arise from this patient's paraprotein-producing cells *(34)*.

Autoantibodies in HIV-1-Infected Individuals

HIV-1-infected individuals have multiple sources of chronic antigenic stimulation, and the high prevalence of hypergammaglobulinemia could be attributed in part to increased production of

antigen-specific antibodies. Alternatively, the in vitro evidence demonstrating that B-cells of HIV-1-infected individuals were maximally activated and spontaneously secreted Ig without evidence of T-cell regulation suggested that antibodies of irrelevant specificity, i.e., autoantibodies, might be produced. This latter hypothesis was supported by early studies documenting the high prevalence of clinically irrelevant antiplatelet antibodies, lupus anticoagulants, and anticardiolipin antibodies in HIV-1-infected individuals. A number of studies have since been undertaken to assess the frequency at which autoantibodies were present and determine their clinical utility in this population. The results of these comparative studies are summarized in Table 1. The general findings of all studies listed in Table 1 were that the presence of autoantibodies were not correlated with or predictive of any clinical disease.

Venereal Disease Research Laboratory (VDRL)

Biologic false-positive (bfp) VDRLs were defined in the studies as positive VDRLs that could not be confirmed by conventional confirmatory tests for syphilis (i.e., MHA-TP or FTA-Abs). bfp VDRLs were detected in 1–17% of HIV-1-infected individuals *(35–37)*.

Erythrocyte Sedimentation Rate (ESR)

ESRs were elevated in 66% of HIV-1-infected individuals in a single study. This high prevalence may not be accurate for the general HIV-1-infected population, since 75% of the patients in this single study had clinical rheumatologic manifestations *(37)*.

Rheumatoid Factor (RF)

RF was present in 21–60% of HIV-1-infected individuals. Titers ranged from 1:40–1:160 *(37,38)*. There was wide disparity between studies in the prevalence of RFs, most likely attributable to different methodologies (e.g., enzyme-linked immunosorbent assays [ELISAs] tended to yield more positive results than traditional latex agglutination-based assays). Of note, RF was detected in 30–58% of HIV-***seronegative*** iv drug users (IVDUs) and hemophiliacs.

Antinuclear Antibody (ANA)

ANAs were detected in 0–23% of HIV-1-infected individuals *(37,39–42)*. If present, titers were generally low. Every immunofluorescent pattern was observed. None of the patients with ANAs had antibodies directed against double-stranded (ds) DNA, SS-A (Ro), SS-B (La), or ribonucleoprotein (RNP).

Antineutrophil Cytoplasmic Antibody (ANCA)

ANCAs were detected in 12–33% of HIV-1-infected individuals *(42)*. The wide range of prevalences was attributable to the different methodologies used to detect ANCAs (e.g., ELISA assays for specific ANCA components [i.e., myeloperoxidase, elastase, proteinase 3] tended to yield more positive results than traditional indirect immunofluorescence-based assays).

Antiglomerular Basement Membrane (GBM) Antibodies

Anti-GBM antibodies were detected in 17% of HIV-1-infected individuals, two-thirds of the plasmas with demonstrable anti-GBM antibodies also contained ANCA *(42)*. The prevalence of anti-GBM antibodies varied with the stage of HIV-1-associated disease.

Antineutrophil Antibodies

Antineutrophil antibodies were detected in 20–75% of HIV-1-infected individuals *(43)*. Prevalence increased in patients with more advanced HIV-1-associated disease. There was no correlation of antineutrophil antibodies with the peripheral neutrophil count.

Antiplatelet Antibodies

Antiplatelet antibodies have been detected in 70–100% of HIV-1-infected individuals, regardless of stage of HIV-1-associated disease *(43,44)*. There was no correlation with the peripheral platelet count.

Anti-Red Blood Cell (RBC) Antibodies

Antibodies bound to RBCs have been detected in 18–34% of HIV-1-infected individuals *(45,46)*. Most of the antibodies were present in low quantities and eluates failed to demonstrate reactivity with specific RBC antigens. There was no correlation with hemolysis.

Lupus Anticoagulant (LAC)

Assays for the detection of LAC are many and varied. Some studies relied on an initial prolongation of the activated partial thromboplastin time (PTT) to identify patients, yet these studies did not consider the wide variability in sensitivity of individual PTT reagents to LAC. Confirmatory tests for LAC included PTT mixing studies, tissue thromboplastin inhibition (TTI), dilute Russell's viper venom test (dRVVT), and platelet neutralization procedure (PNP); these different confirmatory assays are <90% concordant.

Table 1
Prevalence of Autoantibodies in HIV-Seropositive vs HIV-Seronegative Individuals[a]

Test	Ref.	HIV seropositive			HIV seronegative			Comments
		n	No.+	%	*n*	No.+	%	
VDRL	*35*	131	9	7	633	1	0.2	Study population: women
	36	1077	9	1				Study population: military personnel All low titer; 6/9 transient and associated with recent infection No correlation with anticardiolipin antibody, serum IgG or IgA levels
	37	74	13	17	72	0	0	Study population: STD and immunodeficiency clinic patients Rheumatic manifestations observed in 56 (75%) of HIV-seropositive patients, 4 (5%) of HIV-seronegative patients Groups matched for risk factors
ESR	*37*	74	49	66	72	4	5	No stated reference range for ESR
RF	*37*	74	16	21	72	2	2	Nephelometric assay, latex fixation for quantification of RF
	38	20–AIDS	0	0	44–IVDU	13	30	IgM Latex-RF assay
		40–ARC	9	23	19–Homosexual men	3	16	RF titers ranged from 1:40–1:160
		14–IVDU	1	7				
		10–Homosexual men	2	20				
	38	20–AIDS	2	10	Healthy controls			ELISA IgM RF assay
		40–ARC	22	55	40–men	2	5	Lower incidence of IgG and IgA RF with ELISA based assays
		ASx:			40–children	0	0	
		10–Homosexual men	0	0	30–Homosexual men	1	3	

			14–IVDUs	6	43	44–IVDUs	20	45	
			10–Hemophiliacs	6	60	19–Hemophiliacs	11	58	
	ANA	*39*	151	19	13				Study population: consecutive AIDS and ARC patients Assay used a rat liver substrate 2 patients had a 1:160 titer; 17 patients had titers of 1:20 Rim, homogeneous, and speckled patterns were observed No patients had antibodies directed against ds DNA
		40	57	0	0	16	1	6	Study population: 30 AIDS/16 ARC/11 asymptomatic HIV-seropositive Single positive ANA had a titer of 1:140, homogenous pattern
		41	49	0	0				Study population: HIV-infected with musculoskeletal involvement No antibodies against ds DNA, SS-A (Ro), SS-B (La), or RNP detected
		42	105	24	23				Indirect immunofluorescence assay using Hep2 cells No correlation of positive ANA with immunologic status, infection, autoimmune disease, malignancy, or outcome Patterns observed: 21 speckled, 2 homogeneous, 1 nucleolar
		37	74	13	17	72	0	0	Indirect immunofluorescence assay using Hep2 cells Titers $\geq$1:32 considered positive ANA titers low (except one at 1:512)

(*continued*)

Table 1 *(continued)*

Test	Ref.	HIV seropositive *n*	HIV seropositive No.+	HIV seropositive %	HIV seronegative *n*	HIV seronegative No.+	HIV seronegative %	Comments
								Homogeneous pattern in all ANA-positive cases
ANCA	*42*	105	18	17				Indirect immunofluorescence assay No correlation with immunologic status, infection, autoimmune disease, malignancy, or outcome
	42	105	13	12				Neutrophil cytoplasmic extract ELISA No correlation with immunologic status, infection, autoimmune disease, malignancy, or outcome
	42	105	35	33				Antigen specific ELISAs (antiproteinase 3, antimyeloperoxidase, antielastase) No correlation with immunologic status, infection, autoimmune disease, malignancy, or outcome
GBM antibody	*42*	105	18	17				No correlation with stage of disease, infection, presence of anti-GBM disease, malignancy, or outcome Titers borderline–low, except for one moderately high titer
		37–AIDS	5	14				
		32–AIDS	8	25				
		36–Asx	5	14				12 Plasmas also positive for ANCA Presence of anti-GBM antibodies correlated with peripheral CD^{4+} lymphocytes <400/μL
Anti-neutrophil antibody	*43*	16–AIDS	12	75				No correlation with granulocyte count
		7–ARC	5	71				
		10–Asx	2	20				

Antiplatelet antibody	*43*	16–AIDS	16	100				No correlation with platelet count
		7–ARC	5	71				
		10–Asx	7	70				
	44	35	35	100				No correlation with platelet count
Anti-RBC antibody	*45*	55–AIDS	10	18	12,143	78	0.6	No correlation with hemolysis 4 IgG + complement, 2 IgG only, 2 complement only
	46	70	24	34	2000	2	0.1	No correlation with hemolysis No correlation with AZT therapy 23 IgG only, 1 IgG + complement
LAC	*47*	50–AIDS	10	20				PTTs mildly prolonged in all 10 patients PTs mildly prolonged in 3 patients No thrombotic complications noted Transient appearance associated with infection
	48	15	15	100				No bleeding complications One thrombotic episode
ACAs	*40*	30–AIDS	30	100	13–Healthy	0	0	No thrombotic episodes
		16–ARC	16	100	homosexual			4 AIDS patients with high IgM-ACA
		27–Asx	11	41	men			Predominantly IgG-ACA
	53	36	27	75	29	23	79	Hemophiliacs
		(β_2GP1-depend.)	6	17	(β_2GP1-depend.)	4	14	β_2GPI-independence of ACA differentiates HIV-associated ACA from those associated with autoimmune disease
	54	Hospitalized:						No association with prolonged PTT
		72–IgM-ACA	9	13				Incidence of IgM-ACA did not differ significantly between hospitalized vs nonhospitalized HIV-infected patients
		66–IgG ACA	20	30				

(continued)

Table 1 *(continued)*

Test	Ref.	HIV seropositive *n*	No.+	%	HIV seronegative *n*	No.+	%	Comments
		Nonhospitalized:						
		142–IgM-ACA		7				
		142–IgG-ACA		10				
	55				503–IgG-ACA	28	5.6	Study population: normal healthy blood donors
					457–IgM-ACA	38	8.3	No thrombotic events over a 12-mo period No correlation with LAC activity All serum negative for ANA, anti-ds DNA (except one case where RF was detected at low level on one occasion only)
	56	98–IVDUs	47	48	31–IVDUs	2	6.5	No correlation with thrombocytopenia, *P. carinii* pneumonia, disease progression, or clinical stage
		42–Homosexuals	16	38	15-"At risk" heterosexuals	0	0	
		22–Heterosexuals	3	14	50–Healthy controls	0	0	
	37	74–IgG-ACA	70	94	72–IgG-ACA	7	9	30/74 (40%) HIV seropositive had prolonged PTTs vs 2/72 (2%) HIV seronegatives
		74–IgM-ACA	33	44	72–IgM-ACA	2	2	

[a]Abbreviations: ACA, anticardiolipin antibodies; AIDS, acquired immunodeficiency syndrome; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ARC, AIDS-related complex; Asx, asymptomatic; AZT, azidothymidine; β_2GP1, β_2-glycoprotein 1; ELISA, enzyme-linked immunosorbent assay; ESR, erythrocyte sedimentation; GBM, antiglomerular basement membrane antibody; HIV, human immunodeficiency virus; IVDU, iv drug user; LAC, lupus anticoagulant; *n*, number of patients studied; PT, prothrombin time; PTT, activated partial thromboplastin time; RBC, red blood cell; ref., reference number; RF, rheumatoid factor; STD, sexually transmitted disease; VDRL, Venereal Disease Research Laboratory.

Given all the different assays and nonconcordance of their results, LACs were nonetheless detected in 20–71% of HIV-1-infected individuals *(47,48)*; many of the patients also had prolonged PTTs. There were no associated bleeding complications, and only one thrombotic episode has been reported. Of note, at least 25% of the HIV-1-associated LAC did not demonstrate inhibitory activity in mixing studies, and at least 25% failed to demonstrate LAC activity in a dRVVT assay *(49)*.

Anticardiolipin Antibodies (ACAs)

Similar to LACs, discordance between different ACA assays became apparent (overall concordance of ≤59%; *50*). To complicate matters further, protein cofactors (e.g., β2-glycoprotein 1, or b2GP1) necessary for ACA detection in ELISA systems have only recently been recognized *(51)*. Recent studies have in fact demonstrated that b2GP1-dependent binding is more specific for ACA in patients with autoimmune disease (i.e., "autoimmune ACA") than b2GP1-independent ACA observed in patients with infectious diseases (i.e., "alloimmune ACA") *(51)*. Standardization of ACA assays has only recently been undertaken *(52)*. Studies on the prevalence of HIV-1-infected individuals predate these industry-wide attempts at assay standardization, and many of the observed inconsistencies in ACA prevalence may be directly attributable to interassay variability.

ACAs have been detected in 10–94% of HIV-1-infected individuals, and were frequently associated with acute infection, often *Pneumocystis carinii* pneumonia *(37,40,53–56)*. One study demonstrated that the majority of HIV-1-associated ACAs were not b2GP1-dependent *(53)*. Notably, a similar wide range of ACA prevalence was detected in HIV-***seronegative*** controls, including 79% of HIV-seronegative hemophiliacs and 5–10% of normal healthy blood donors *(53)*.

Other Autoantibodies

Antibodies directed against a conformational epitope present on HIV-1 envelope gp41 crossreacted with astrocytes, leading to a hypothesis that molecular mimicry might contribute to HIV-1-associated neurologic syndromes *(57,58)*. The clinical significance of these and other autoantibodies detected in HIV-1-infected individuals *(59)* is unclear owing to the lack of studies to assess their prevalence and clinical correlation.

A combinatorial antibody library approach was undertaken to assess the autoimmune repertoire expressed in HIV-1-infected individuals *(60)*. A panel of 38 monoclonal antibodies (MAbs) generated by this technology using bone marrow B-cells from asymptomatic HIV-1-infected individuals demonstrated moderate affinity and marked

crossreactivity with a variety of self-antigens *(60)*. In contrast, only high-affinity autoantibodies reactive with a single autoantigen were recovered from similarly constructed antibody combinatorial libraries created with B-cells obtained from a patient with autoimmune disease *(60)*. These data demonstrated that auto- and broadly reactive antibodies produced by HIV-1-infected individuals are more consistent with those detected in normal healthy individuals and differ from "classic" autoantibodies in patients with autoimmune disease. The significance of this finding, however, is unclear given that this recombinant approach to antibody isolation will produce all possible combinations of H and L chains for which the original mRNA coded, with no assurance that the specific H and L chain combination in the antibodies characterized in this study actually existed in vivo.

Evidence for Normal B-Cell Function in HIV-1-Infected Individuals

Given all the evidence for dysregulated and dysfunctional B-cells in HIV-1-infected individuals, additional studies have been directed at determining if there is normal B-cell function in HIV-1-infected individuals. The majority of this information arose from early vaccine trials aimed at conferring or boosting immunity to common pathogens that caused more severe and frequently disseminated infection in HIV-1-infected individuals.

Vaccine Trials

Vaccine trials have been conducted with *S. pneumoniae* capsular polysaccharide, *H. influenzae* type B capsular polysaccharide diphtheria protein toxoid conjugate, tetanus toxoid, and influenza virus *(61–67)*. Responses to vaccines were determined by measuring increases in antibodies directed against the specific immunogen. The results of these trials were mixed, with some studies showing no difference in antibody response between HIV-1-infected individuals and healthy uninfected controls, and others showing blunted or marked differences in antibody responses. A trend toward decreased antibody response associated with increased severity of HIV-1 disease was variably observed. Despite these inconsistencies between studies, they did demonstrate that normal B-cell responses to vaccines could be elicited in HIV-1-infected individuals.

Whether or not the antibodies elicited were in fact protective could not be determined, since absolute antibody titers deemed to confer protection have not been defined and since long-term outcome studies for individuals with known antibody titers after vaccination with pathogens have not been conducted.

Anti-HIV Antibodies

Molecular analysis of V_H genes of anti-HIV antibodies derived from hybridomas created from circulating B-cells of HIV-1-infected individuals revealed a high degree of nucleotide substitution, with a pattern consistent with that expected for somatic hypermutation *(68–71)*. These data from individuals chronically stimulated with HIV-1 support observations from vaccine trials that normal B-cell responses to antigenic challenge—whether acute or chronic—were maintained in HIV-1-infected individuals.

Link of Autoimmunity with HIV-1-Associated B-Cell Lymphomas

A high prevalence (i.e., 5–10%) of non-Hodgkin's B-cell lymphomas has been observed in the HIV-1-infected population *(72,73)*. Unlike other B-cell lymphomas occurring in non-HIV-infected individuals, cofactors implicated in B-cell transformation (such as EBV infection and c-*myc* translocation) have not been uniformly present in HIV-1-associated lymphomas. A multistep pathogenesis model has been proposed for HIV-1-associated lymphomas, wherein chronic antigenic stimulation (e.g., EBV, CMV, HIV-1, self-antigens) of B-cells provides a rapidly proliferating population at risk for additional genetic events leading to the emergence of a malignant clone *(74)*. Support for this hypothesis is provided by molecular analysis of IgMs produced by the five different HIV-1-associated lymphomas that have been characterized to date; two of these IgMs were reactive with "i" antigen (an autoantigen on human erythrocytes), one with dsDNA and actin, one with HIV-1 gp41, and the antigenic specificity of the last Ig undetermined *(75–77)*. The IgMs reactive with "i" antigen exhibited high-affinity and avidity, and additional reactivity with other common autoantigens could not be demonstrated. The V_H genes of these five lymphoma associated IgMs were $\leq$95% homologous to their germline V_H genes of origin, and all five had significant nucleotide changes occurring in a pattern consistent with a somatic hypermutation process, suggesting that these clones may have been antigen-selected.

In summary, HIV-1-infection is associated with widespread abnormalities in the host immune system, some of which are reflected in the numerous B-cell abnormalities discussed in this chapter. The high prevalence of clinically irrelevant autoantibodies and the demonstration of spontaneous secretion of Igs at maximal capacity suggest a link with these baseline B-cell abnormalities induced by HIV-1-infection with the high prevalence of HIV-1-associated B-cell lymphomas and the demonstration that lymphoma IgMs were reactive with chronically present antigens (i.e., self, HIV-1 gp41, or others).

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Rheumatologic Manifestations of HIV Infections

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Introduction

The clinical manifestations of human immunodeficiency virus (HIV) infections are myriad. Musculoskeletal problems plague up to 72% of HIV-infected individuals *(1)*. Rheumatologic complications can occur at any time during the course of HIV disease, and such rheumatologic conditions as Reiter's syndrome, psoriatic arthritis, polymyositis, and necrotizing vasculitis may sometimes be the first clinical clue to the presence of HIV infection *(2)*. Nonspecific arthralgias and myalgias are common features of primary HIV infections.

This chapter focuses on the rheumatologic manifestations of HIV infections, including arthritis (*see* Table 1), myopathies, vasculitis, sicca syndrome, and other autoimmune phenomena. Although some of these features, such as necrotizing vasculitis, can be life-threatening, others, such as severe arthritis or polymyositis, may greatly impair the quality of the patient's life. Furthermore, such drugs as methotrexate, azathioprine, and cyclophosphamide, which are commonly used to treat rheumatologic conditions, may in fact hasten the development of opportunistic infections in HIV-infected individuals. Consequently, one must be especially vigilant in managing these conditions.

Arthritis

Reiter's Syndrome and Reactive Arthritis

Epidemiology

Reiter's syndrome and other spondyloarthopathies are probably the most common types of arthritis to affect HIV-infected individuals. In careful studies of consecutive, unselected HIV-infected patients per-

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Table 1
Arthropathies Associated with HIV Infection

Spondyloarthropathies
Reiter's syndrome *(8,9)*
Psoriatic arthritis *(23)*
Undifferentiated spondyloarthropathy *(148)*
HIV-associated arthritis *(1,12,26–28)*
Septic arthritis *(75)*
Gouty arthritis *(149)*
Painful articular syndrome *(1,35,36)*
Rifabutin-induced arthralgia/arthritis *(150)*
Arthralgias *(2)*
Aseptic necrosis *(37–41)*
Hypertrophic osteoarthropathy *(151–153)*
Dupuytren's contracture *(154,155)*
Lumbar radiculopathy *(156)*

formed in Tampa, FL, New York City, Cleveland, Buenos Aires, Toronto, and Mexico City the prevalence of Reiter's syndrome has been estimated at 2–10% *(3,4)*. These figures, however, are somewhat controversial. Large-scale epidemiologic studies performed by questionnaires in San Francisco, Baltimore, and Cincinnati have indicated a prevalence of Reiter's syndrome of 0.1–0.5%, figures similar to that found in the general population *(5–7)*.

Clinical Features

Reiter's syndrome in HIV-infected individuals has similar clinical manifestations to idiopathic Reiter's syndrome *(2,8,9)*. These patients tend to have a severe, persistent oligoarthritis primarily affecting the large joints of the lower extremities. Enthesopathies of the Achilles tendon, plantar fascia, and anterior and posterior tibial tendons are common and can be quite severe. These enthesopathies combined with multidigit dactylitis of the toes may prevent weight bearing or cause the patients to walk with a characteristic gait with the feet in inversion and extension in an attempt to distribute weight on the lateral margins of the feet. This gait has been termed the "AIDS gait" *(10)*. A few HIV-infected patients with Reiter's syndrome have been reported to have sacroiliitis, although the majority do not *(8,11)*. Urethritis has been found in 59% of HIV-infected individuals with Reiter's syndrome, conjunctivitis in 47%, keratodermia blennorrhagicum in 25%, and circinate balanitis in 29% *(2)*. Oral ulcers have also been noted *(2)*. The signs and symptoms of Reiter's syndrome have occurred before or simultaneous with the onset of clinical immunodeficiency in about two-thirds of patients with HIV infections *(2)*. Thus, the presence of Reiter's syndrome may be a clinical clue to the diagnosis of HIV infection in some

individuals. Consequently, patients presenting to a physician with Reiter's syndrome or reactive arthritis should be questioned about HIV risk factors, such as sex with other males, unprotected sex with many partners, iv drug abuse, and blood transfusions.

Seventy-three percent of HIV-infected individuals with Reiter's syndrome from North America are HLA-B27 positive, a proportion similar to that found in idiopathic Reiter's syndrome *(2)*. In contrast, HLA-B27 has not been detected in any of 13 Black patients with Reiter's syndrome and HIV infection *(12,13)*, possibly reflecting either the low prevalence of HLA-B27 in Blacks in general and in Black patients with Reiter's syndrome in particular, or different causative agents or mechanisms in Black patients *(2)*.

Some patients with a Reiter's-like arthritis lack urethritis and conjunctivitis and, thus, are more properly classified as having "reactive arthritis." The articular manifestations and triggering organisms found in patients with reactive arthritis are very similar to those in Reiter's syndrome. Reiter's syndrome is in fact a part of the reactive arthritis spectrum. Clinical features that tend to differentiate reactive arthritis, including Reiter's syndrome, from other types of arthritis include oligoarticular involvement of the lower extremities, enthesopathies, antecedent diarrheas or venereal illnesses, and HLA-B27 positivity.

Etiology

Although organisms known to trigger Reiter's syndrome or reactive arthritis, such as *Salmonella typhimurium, Shigella flexneri, Campylobacter fetus, Ureaplasma urealyticum,* and yersinia species have been found in less than one-third of HIV-infected patients with reactive arthritis, many HIV-infected individuals with Reiter's syndrome and reactive arthritis have an antecedent culture-negative diarrheas illness *(2,8,11,14)*.

The relationship among Reiter's syndrome, reactive arthritis, and HIV infection suggests a biologic association among the three entities, although the actual connection is unknown and subject to speculation. It is certainly possible that a coincident infection by sexually transmitted agents, such as *Chlamydia trachomatis* and *U. urealyticum,* along with HIV in a group of patients who are at risk for sexually transmitted diseases can cause both Reiter's and HIV infection *(2,8)*.

It is possible that either the HIV-induced immunodeficiency itself or the increase in CD8 lymphocytes caused by the HIV infection can help to initiate aberrant immune responses, which lead to Reiter's syndrome or reactive arthritis. Alternatively, immunodeficiency resulting from the HIV infection may predispose to the acquisition of arithrogenic organisms. Furthermore, a novel bowel pathogenic organism may be more prevalent in HIV-infected patients with diarrhea that can trig-

ger the onset of Reiter's syndrome or reactive arthritis. Finally, the activation of the immune response with Reiter's syndrome may convert a latent HIV infection into full-blown AIDS *(2,8)*.

Management

Management of HIV-infected patients with Reiter's syndrome and reactive arthritis can be difficult. There have been no formal clinical trials conducted on the treatment of HIV-infected patients with Reiter's syndrome. Thus, treatment has usually paralleled treatment of Reiter's syndrome in non-HIV-infected individuals.

Many of these patients do not respond well to nonsteroidal anti-inflammatory drugs (NSAIDs), and maximum or near-maximum doses need to be employed for optimal clinical benefit. If traditional NSAIDs in maximal doses prove to be ineffective, some authorities have used phenylbutazone starting with 100 mg three times a day and increasing to 400–600 mg daily if needed *(15)*. The complete blood count needs to be monitored every few weeks in patients taking phenylbutazone. Despite having several patients taking concomitant phenylbutazone, zidovudine gazidothymidine [AZT]), and/or sulfasalazine, Solomon et al. *(15)* did not found any cytopenias in their phenylbutazone-treated patients.

In general, low-dose corticosteroid have not been found to be beneficial in HIV-infected individuals with Reiter's syndrome. Solomon et al. *(15)* noted symptomatic relief with 40 mg or more of oral prednisone. The prompt and frequent development of moniliasis, however, limits the use of this therapy. Intra-articular corticosteroid injections usually provide effective symptomatic control, and can be a very practical treatment when one or two joints or entheses are involved. The benefits from corticosteroid injections can be augmented by immobilizing the injected joint with a splint for 5–7 d after injection *(15)*. Although secondary septic arthritis from intra-articular steroid injections does not seem to be a significant problem in HIV-infected individuals, the patient should be instructed to watch carefully for signs of infection.

Disease-modifying antirheumatic drugs have been employed in the treatment of HIV-infected individuals with Reiter's syndrome. Although no controlled studies have been performed, Solomon et al. *(15)* reported that about one-third of their HIV-infected patients with Reiter's syndrome did respond to sulfasalazine in doses ranging from 1–3 g daily. Others have reported similar results *(16,17)*. Although sulfa allergies are common in HIV-infected individuals, sulfasalazine-allergic patients can be desensitized to the drug *(15)*.

Intramuscular gold has been anecdotally reported to be effective in a single patient with HIV-associated Reiter's syndrome *(15)*. Anec-

dotal reports suggest that hydroxychloroquine fails to ameliorate the symptoms in this condition *(15)*. At least two patients with Reiter's syndrome and AIDS benefited from treated with etretinate *(18,19)*.

Virtually every HIV-infected patient who has been treated with methotrexate for Reiter's syndrome or psoriatic arthritis has contracted *Pneumocystis carinii* pneumonia or Kaposi's sarcoma, shortly after the institution of the methotrexate *(8,11,20)*. There are, however, three reports of successful treatment with methotrexate of psoriatic arthritis in HIV-infected patients without the development of opportunistic infections *(21,22)*. One azathioprine-treated individual developed profound fatigue and weight loss that resolved on the discontinuation of this drug *(8)*. Thus, methotrexate and azathioprine should not be routinely used in HIV-infected patients with reactive arthritis.

Solomon et al. *(15)* employed cyclosporine A under an experimental protocol in five HIV-infected patients with Reiter's syndrome and persistent articular symptoms despite treatment with phenylbutazone and sulfasalazine. They used an initial dose of 1 mg/kg, with careful titration to 2–4 mg/kg as needed. Two patients showed complete remission, and three patients demonstrated partial remission. Lymphocyte subsets did not change significantly, and CD4 lymphocyte counts did not drop. None of the patients developed renal insufficiency, hypertension, cytopenia, or opportunistic infections while on cyclosporine A.

Treatment with zidovudine (AZT) has generally not proven to be beneficial in HIV-infected individuals *(15)*. Physical therapy and adaptive devices, such as canes and walkers, can greatly enhance the quality of many of these patients' lives, especially in patients with an "AIDS gait."

Other Spondyloarthropathies

Psoriatic Arthritis

Psoriatic arthritis has also been reported in greater frequency in HIV-infected individuals than in the general population. Prevalences of 2–6% in unselected HIV-infected individuals have been reported *(3,9)*. Psoriasis without arthritis is also more common in HIV-infected individuals than in the general population.

HIV-infected individuals with psoriatic arthritis tend to have severe, painful oligoarthritis, predominantly affecting the lower extremities. Sausage digits in the feet, as well as heel and foot enthesitis, are commonly present *(23)*. Psoriatic lesions of various types, including vulgaris, guttate, sebopsoriasis, pustular, and exfoliative erythroderma, may all be found in HIV-infected patients with psoriatic arthritis. Sometimes more than one type of psoriatic skin lesion may be found in the

same patient *(23)*. Interestingly, sacroiliac involvement and uveitis may occur less commonly in the HIV-infected individual with psoriatic arthritis than in the non-HIV-infected psoriatic arthritic patient *(23)*.

Management of psoriatic arthritis in the HIV-infected individual is empiric, since no well-controlled studies have been published. Many patients will obtain symptomatic relief from the use of NSAIDs. Frequently, the maximum recommended dose of these medications is needed in order to provide patients with effective symptomatic relief. On occasion, phenylbutazone in doses of 100-mg tablets two to three times a day is effective when safer NSAIDs are ineffective. Careful monitoring of the complete blood count should be undertaken when using phenylbutazone *(15,23)*.

Etretinate may be helpful in some HIV-infected patients with psoriatic arthritis *(15)*. The use of psoralen and pulsed UV actinotherapy (PUVA) benefited the skin and joints of one HIV-infected individual with psoriatic arthritis *(11)*. Zidovudine, has produced skin clearing in some patients with psoriasis, but has been less consistently successful in treating psoriatic arthritis *(23,24)*. As previously mentioned, methotrexate and azathioprine should be avoided in HIV-infected individuals because of the high incidence of opportunistic infections *(2,15,20,23)*. Recently, however, three patients with HIV infection and psoriatic arthritis had good clinical results from methotrexate treatment without the development of opportunistic infections *(21,22)*. Another HIV-infected patient has demonstrated marked improvement with cyclosporin A administration for psoriatic arthritis *(25)*.

Other Spondyloarthropathies

There are some HIV-infected individuals with features common to spondyloarthropathies, such as enthesopathies, oligoarthritis, and onychodystrophy, but lacking the full clinical features of Reiter's syndrome or psoriatic arthritis. These patients are often referred to having an "undifferentiated spondyloarthropathy," and are probably part of a spectrum of spondyloarthropathic conditions, including Reiter's syndrome, reactive arthritis, and psoriatic arthritis. The management of undifferentiated spondyloarthropathies in the setting of HIV infection is identical to that of HIV-infected individuals with Reiter's syndrome, reactive arthritis, and psoriatic arthritis. Ankylosing spondylitis and the arthritis of inflammatory bowel disease, two other forms of spondyloarthropathy, do not seem to be associated with HIV infection *(23)*.

HIV-Associated Arthritis

Clinical Features

In 1988, Rynes et al. *(26)* described the first four cases of new, apparently AIDS-associated arthritis. Their patients had a subacute

oligoarthritis primarily involving the knees and ankles. The arthritis was characterized by relatively brief bouts of extreme disability and pain. The peak intensity of the pain occurred within 1–4 wk. The arthritis remitted after 6 wk to 6 mo. Synovial fluid removed from these patients was noninflammatory. Synovial biopsies revealed chronic mononuclear infiltrates in contrast to the polymorphonuclear leukocytic infiltrates typically seen in inflammatory arthritis. None of these patients had antecedent infections, mucocutaneous lesions, or radiographic evidence of sacroiliitis. All patients tested negative for the HLA-B27 antigen, rheumatoid factor, and antinuclear antibodies *(26)*. Similar cases of HIV-associated arthritis have been subsequently described *(1,12,27,28)*.

Pathophysiology

The pathophysiologic mechanism of HIV-associated arthritis is unknown. Low synovial leukocyte counts and tubuloreticular inclusions seen in some patients with HIV-associated arthritis by electron microscopy suggest a direct viral infection of the joint *(26)*. Furthermore, not only have researchers isolated HIV from synovial fluid of HIV-infected individuals, but electron microscopy has revealed retroviral-like particles in the synovial fluid *(27,28)*. Other viruses, including rubella virus, cytomegalovirus, and herpes simplex virus type I, are known to cause arthritis by direct invasion of synovial tissue *(2)*. Furthermore, another retrovirus, the caprine arthritis-encephalitis virus, causes chronic arthritis in goats *(29)*.

Immune-complex deposition in the joint, which occurs with hepatitis B and rubella viral-induced arthritis, may be another possible mechanism for the pathogenesis of HIV-related arthritis *(2)*. Rynes et al. *(26)* noted immunoglobulin depositions in the synovial biopsy specimens of patients with arthritis. Except for one patient with anticardiolipin antibodies, however, no serologic tests indicative of autoantibody or immunecomplex formation have been noted in these individuals *(2,26)*.

A final proposed mechanism for the occurrence of HIV-associated arthritis is that the HIV-associated arthritis may in fact represent a form of reactive arthritis. The reported patients with HIV-associated arthritis, however, lacked antecedent genitourinary or enteric infections, urethritis, conjunctivitis, mucocutaneous lesions, sacroiliac erosions, HLA-B27 antigen, and inflammatory synovial fluid, all of which are important and defining clinical features of reactive arthritis and Reiter's syndrome *(1,2,26)*.

Treatment

NSAIDs have successfully and promptly ameliorated pains and inflammation in most patients with HIV-associated arthritis *(12,26)*, but

not in all *(28)*. No other management strategies have been reported. Because of occasional past success with NSAIDs, I favor a 3–6 wk trial of at least three different NSAIDs, discontinuing them if no benefit is observed. Intra-articular corticosteroid injections can be used for particularly symptomatic joints. Hydroxychloroquine has proven beneficial in two patients with HIV-associated arthritis *(30)*.

Other Arthropathies

Septic Arthritis

Not surprisingly, septic (bacterial) arthritis may also accompany HIV infections. Individuals infected with HIV are predisposed to developing both opportunistic and nonopportunistic infections. Septic arthritis should be suspected in any HIV-infected individual with an acutely swollen joint. Intravenous drug addicts may have infections in unusual joints, such as the sternoclavicular and sacroiliac joints *(31,32)* and discs *(33)*. Synovial fluid from HIV-infected individuals with subacute and chronic arthritis should be aspirated and cultured before attributing such arthritides to a noninfectious cause, since these individuals may be infected with fungi, mycobacteria, or even bacteria. Sometimes synovial biopsies are necessary to isolate fungi and mycobacteria from joints.

Many types of bacteria, mycobacteria, and fungi have been isolated from septic joints in HIV-infected individuals (*see* Table 2). *Staphylococcus aureus is* the most common etiologic agent in HIV-infected patients with septic arthritis. Organisms, such as fungi and mycobacteria, which usually cause chronic infectious arthritis in HIV-uninfected individuals, may result in acute or subacute infectious arthritis in HIV-infected patients.

The same organisms that cause septic arthritis in HIV-infected individuals have also been noted to cause septic bursitis and osteomyelitis. Septic arthritis and osteomyelitis sometimes coexist; therefore, imaging studies, such as serial radiographs and/or radionuclide bone scans, should be performed in patients with septic arthritis to eliminate the possibility of coexistent osteomyelitis.

Therapy for infectious arthritis in HIV-infected patients does not differ from the treatment of infectious arthritis in other immunocompromised hosts. HIV-infected patients with septic arthritis should be treated parenterally with appropriate antibiotics for 4–8 wk. Some physicians may choose to treat septic arthritis patients who are doing well clinically with oral antibiotics after 2–3 wk of treatment with parenteral antibiotics. However, the efficacy of oral antibiotic therapy for septic arthritis has not been well established for all bacterial pathogens. The choice of all antibiotics should be based on the culture and

Table 2
Organisms Reported to Cause Septic Arthritis
in HIV-Infected Patients

Bacteria
- *Bacteroides melaninogenicus (157)*
- *Borrelia burgdorferi (158)*
- *Campylobacter jejuni (159)*
- *Hemophilus influenzas* type B *(160–163)*
- *Helicobacter cinaedi (164)*
- *Klebsiella species (165)*
- *Neisseria gonorrhea (148,157,162,166–171)*
- *Pseudomonas* species *(171)*
- *Rhodococcu.s erythropolis (172)*
- *Salmonella choleraesuis (173,174)*
- *Salmonella enteritidis (77,171,175,176)*
- *Salmonella typhimurium (177)*
- *Staphylococcus aureus (75,148,157,167,170,171,176,178–181)*
- *Staphylococcus epidermidis (157,179)*
- *Streptococcus equisimilis (157)*
- *Streptococcus pneumonias (173,181,182)*
- *Streptococcus sanguis (157)*
- *Streptococcus viridans (157)*
- *Treponema pallidum (183,184)*

Mycobacteria
- *Mycobacterium avium (185–187)*
- *Mycobacterium hemophilum (182,188)*
- *Mycobacterium kansasii (148,171,189)*
- *Mycobacterium tuberculosis (148,157,167,179,180)*

Fungi
- *Candida albicans (33,43,157,179,190,191)*
- *Coccidioides immitis (192)*
- *Cryptococcus bertholletiae (75)*
- *Cryptococcus neoformans (193)*
- *Cunninghamella bertholletiae (194)*
- *Histoplasma capsulatum (35,75,148,171)*
- *Mucor* species *(157,179)*
- *Nocardia asteroides (195)*
- *Sporothrix schenckii (196)*

sensitivity of the organism involved once such information becomes available. Infections with fungi or mycobacteria invariably often require longer periods of antimicrobial therapy.

Patients with septic arthritis should have an arthrocentesis with complete drainage of the joint performed once or twice a day as long as the synovial fluid seems to reaccumulate after the arthrocentesis. The synovial fluid should be checked for a cell count daily. A daily decrease in the synovial fluid white blood count usually indicates satisfactory treatment of septic arthritis.

If the synovial fluid white blood count does not continue to decrease on a daily basis or if closed-needle aspiration does not provide complete drainage of the synovial fluid, surgical drainage of the infected joint fluid either by arthroscopy or by open arthrotomy should be considered *(34)*. Patients with septic bursitis usually can be managed with closed-needle drainage and antibiotic therapy alone, without the need for surgery.

Painful Articular Syndrome

Berman et al. *(1)* at the University of South Florida in Tampa, described 10 patients with acute, severe, and intermittent articular pain. Other cases have been subsequently reported *(35,36)*. These patients developed the sudden onset of debilitating arthralgias in three or fewer joints without exhibiting clinical evidence of synovitis. The articular pain lasted from 2–24 h. In many cases, NSAIDs did not adequately control the pain, and narcotics needed to be administered *(1)*. This painful articular syndrome appears to be unique in HIV-infected patients, but needs to be differentiated from aseptic necrosis, which has been reported to occur with some frequency in HIV-infected patients, even in multiple sites *(37–41)*.

Rheumatoid Arthritis

Rheumatoid arthritis has not been associated with HIV infection. Considering that the prevalence of rheumatoid arthritis is about 1% in the general population, it is surprising that there are only 15 case reports of rheumatoid arthritis in HIV-infected individuals in the medical literature *(13,42–52)*. One possible reason for the lack of association is epidemiologic. Rheumatoid arthritis occurs more frequently in women, whereas in Western countries, HIV infection mostly afflicts men *(2)*. There may beg however, a direct relation between HIV infection and the paucity of patients with rheumatoid arthritis. Rheumatoid joints have an increase in CD4-positive T-lymphocytes and a decrease in CD8-positive T-lymphocytes. This T-lymphocyte ratio may be of significance in the pathogenesis of rheumatoid arthritis. Infection with HIV is associated with a decrease in CD4-positive T-lymphocytes and a relative increase in CD8-positive T-lymphocytes, a phenomenon that may prevent development of rheumatoid synovitis *(2)*. In fact, many of the HIV-infected rheumatoid arthritis patients appear to go into remission as the result of the HIV infection *(42,44,45)*. It is of interest that treatment of rheumatoid arthritis with anti-CD4 monoclonal antibodies (MAbs) has induced remission in patients with rheumatoid arthritis *(45)*.

Other patients with coexistent HIV infection and rheumatoid arthritis have had continued joint destruction from rheumatoid arthritis, thus implying that rheumatoid arthritis activity does not require the presence of significant numbers of CD4-positive T-lymphocytes *(52)*.

Table 3
Myopathies Associated with HIV Infection

Polymyositis *(53–55)*
Dermatomyositis *(53,54)*
Zidovudine-induced myositis *(62–67)*
Necrotizing noninflammatory myopathy *(197)*
Pyomyositis *(75)*
Infectious myositis with opportunistic organisms *(70,96,198)*
Nemaline (rod) myopathy *(58,199,200)*
Rhabdomyolysis *(201–203)*
Fibromyalgia *(100,101)*
Myositis ossificans *(204)*
Forearm compartment syndrome *(205)*
Myasthenia Gravis *(206,207)*
Subclinical myopathy *(97)*
Muscle wasting *(98,99)*
Non-Hodgkin's lymphoma of muscle *(208,209)*
Leiomyoma of muscle *(210).*
Leiomyosarcoma of muscle *(210)*
Kaposi's sarcoma of muscle *(198)*

Arthralgias

Diffuse arthralgias are a common manifestation of acute HIV infection, which causes such additional infectious mononucleosis-like symptoms as fever, sore throat, headache, myalgia, abdominal cramps, diarrhea, and lymphadenopathy *(2)*. Arthralgias may occur at other times during the course of the HIV infection as well.

The arthralgias in HIV-infected individuals can usually be well controlled with simple analgesics, such as acetaminophen, or with NSAIDs. Physical measures, such as the localized application of heat or ice, can also add to symptomatic relief.

Myopathies

Polymyositis

Clinical Features

Several different types of myopathies have been reported in people infected with HIV (*see* Table 3), with inflammatory myopathies resembling idiopathic polymyositis being the most commonly reported type *(2)*. Patients with HIV-associated inflammatory myopathy typically have a subacute onset of proximal muscle weakness (especially in the lower extremities), myalgias, and some limb muscle wasting *(2,53)*. In contrast to idiopathic polymyositis, dysphagia and shortness of breath have not been reported in HIV-infected individuals with myositis *(53)*.

Typical skin lesions of dermatomyositis on both the face and hands have also been seen in HIV-infected patients *(53,54)*. In some individuals, the symptoms of polymyositis have been the first clinical feature of the patient's HIV infection to become clinically evident *(55)*. Virtually all cases of polymyositis in HIV-infected individuals have been associated with serum creatinine kinase levels five to six times higher than normal *(2)*. Electromyographic studies in these patients have shown evidence of myopathy, and clinical testing usually showed muscle weakness *(2)*.

The pathologic features seen in muscle biopsy specimens in patients with HIV-associated polymyositis strongly resembles that of idiopathic polymyositis, including such features as inflammatory infiltrates with evidence phagocytosis and fiber necrosis *(2)*. Other pathologic features that have been reported include cytoplasmic bodies, variation in fiber size, multinucleated giant cells, and central rod bodies *(2)*.

The pathologic features seen in muscle biopsy specimens in patients with HIV-associated polymyositis strongly resemble that of idiopathic polymyositis, including such features as inflammatory infiltrates with evidence of phagocytosis of muscle fibers and fiber necrosis *(2)*. Other pathologic features that have been reported include cytoplasmic bodies, variation in fiber size, multinucleated giant cells, and central rod bodies *(2)*.

Pathogenesis

The exact pathogenetic mechanism of polymyositis in HIV-infected individuals is not known. Other viruses, such as influenza types A and B, coxsackievirus, echovirus, rubella, and HTLV-I, have been associated with polymyositis *(2,56)*. One possible pathogenetic explanation is the direct infection of muscle cells by HIV. In vitro studies seem to support this hypothesis. In contrast, in vivo experiments using monkeys infected with simian retrovirus type I (a retrovirus closely related to HIV that produces polymyositis in monkeys) have shown that HIV can be found in inflammatory cells surrounding or invading muscle fibers, but not directly in the muscle fibers themselves *(57)*. Furthermore, with the exception of one report of the presence of HIV-p24 antigen in the cytoplasm of degenerating muscle fibers *(53)*, most investigators have not detected viral antigens or particles by immunocytochemical analysis or by electronmicroscopy in muscle fibers, nor have they successfully cultured HIV from affected muscle tissue in patients with HIV-associated polymyositis *(53,55,58,59)*.

A second postulated etiologic mechanism for polymyositis in HIV-infected patients is an HIV-triggered immune-mediated mechanism leading to the invasion of muscle fibers by lymphoid cells. The presence of a mononuclear inflammatory cell infiltrate, with the presence of

CD4- and CD8-positive lymphocytes in the involved muscle lends support to this hypothesis *(53)*. Dalakas *(60)* reported that the predominant endomysial cells in HIV-associated polymyositis are $CD8^+$, nonviral-specific cytotoxic T-cells which along with macrophages invade or surround major histocompatibility complex (MHC) class I antigen-expressing nonnecrotic muscle fibers.

A third possible etiology of polymyositis in HIV-infected individuals is an inflammatory immune response to an antigen from an opportunistic organism, HIV, or both. This conjectured antigen, which would be present in the interstitial fibroblast as well as on the infecting organism, may serve as a crossreacting antigen, which in turn would trigger an attack on the myocytes by cells of the immune system, leading to necrosis and phagocytosis *(53,55,61)*. Finally, myositis may be a direct consequence of immunodeficiency itself *(61)*.

Treatment

Most patients with HIV-related polymyositis have responded to treatment with prednisone in doses ranging from 30–60 mg daily for 8–12 wk with improved strength and a decrease in serum creatinine kinase levels *(2,53)*. Patients with HIV-associated polymyositis and dermatomyositis often take longer to show clinical and biochemical improvement in their disease than patients with the idiopathic form of the disease *(53)*. Although most patients have tolerated corticosteroid without the development of significant side effects, two patients have developed opportunistic infections within a few weeks of taking steroids for polymyositis *(55)*. As previously mentioned, methotrexate and azathioprine should not routinely be used as steroid-sparing agents in HIV-infected individuals because of the high incidence of subsequent opportunistic infections and cancers *(2,8,15,20,23)*.

Zidovudine-Induced Myositis

The antiretroviral zidovudine (formerly known as AZT) induces a polymyositis-like clinical picture *(62)*. These patients also present to physicians with proximal muscle weakness 3–21 mo after starting zidovudine. They typically have a two- to sixfold elevation in serum creatinine kinase levels, as well as proximal muscle weakness on physical examination *(62–67)*.

Pathologically, zidovudine-induced myositis is quite difficult to distinguish from idiopathic or HIV-associated polymyositis by light microscopy. It can, however, be distinguished by the appearance of "ragged-red" fibers, indicative of a mitochondrial abnormality, on electron microscopy. This mitochondrial abnormality may be induced by zidovudine *(62)*. Diagnostically, histochemical reaction for cytochrome-c-oxidase has proven to be more sensitive than examination for "ragged-

red" fibers to evaluate zidovudine muscular toxicity *(68)*. Noninvasive detection is possible by evaluating the lactate–pyruvate ratio in the blood *(69)*.

The mechanism of mitochondrial toxicity is not fully understood. Zidovudine is a thymidine analog that can act as a chain terminator when incorporated into a growing DNA strand. Phosphorylated zidovudine also competitively and noncompetitively inhibits mitochondrial DNA (mtDNA) polymerase-γ, which could be a basis for toxicity of the drug *(70)*. A consistent depletion of mtDNA has been observed in patients with zidovudine myopathy *(71)*. Other cofactors, such as selenium deficiency and interleukin-1, may be partially responsible for the development of zidovudine myopathy *(70)*.

Seven of the 15 patients in Dalakas et al.'s *(62)* study of zidovudine-induced myositis showed muscle strength improvement and normalization of serum creatinine kinase levels 7–10 d after the simple elimination of zidovudine. Two patients showed clinical improvement with the use of NSAIDs along with the discontinuation of zidovudine. Four patients required the use of oval corticosteroid to achieve clinical improvement in their myopathies. These patients may have had coexistent HIV-associated polymyositis with their zidovudine-induced myositis. The remaining two patients in the study died of AIDS-related causes before their myopathy resolved *(62)*. Other investigators have shown a similarly good prognosis *(63,64,67,72)*. 2',3'-dideoxyinosine (ddI) and 2',3'dideoxycytidine (ddC) are apparently safe alternatives in patients with zidovudine-induced myopathy *(73)*.

Other Myopathies

Pyomyositis, solitary or multiple muscle abscesses that are not formed by local extension from superficial subcutaneous tissues, have been reported in HIV-infected patients. These abscesses can be sterile, or if they are nonsterile, they usually contain *S. aureus (74–86)*. Imaging techniques, such as ultrasound, computed tomography, or magnetic resonance imaging *(87)*, are helpful in identifying and localizing the abscess or abscesses, and may guide a needle aspiration for identification of the pathogenic organism. Treatment of pyomyositis should be promptly instituted using iv antibiotics along with open surgical drainage and debridement when indicated *(75)*. In addition, muscle fibers can be directly infected by opportunistic organisms, such as *Toxoplasma gondii (88)*, *Cryptococcus neoformans (89)*, *Mycobacterium avium intracellulare (90)*, microsporidia *(91)*, *Escherichia coli (92)*, *Trichinella spiralis (93)*, group C streptococcus *(94)*, *Citrobacter freundii (74)*, and cytomegalovirus *(70,95,96)*.

Comi et al. *(97)* reported a subclinical myopathy in 11 of 15 consecutive unselected patients with AIDS. Abnormal electromyographs

in the presence of normal clinical examinations and the lack of complaints of muscle pain or weakness characterized these 11 patients. Biopsy samples from the biceps brachii muscle showed nonspecific signs of primary muscle involvement in four patients. Two of these patients also had findings that indicated associated muscle denervation.

The HIV muscle-wasting syndrome frequently affects patients with full-blown AIDS. It has been defined as the unintentional loss of more than 10% of body weight, plus either chronic diarrhea or chronic weakness and documented fever, in the absence of a concurrent illness or condition other than HIV infection that could explain the finding *(98)*.

The HIV muscle-wasting syndrome is so commonly seen in HIV-infected patients in parts of Africa that AIDS is termed "slim disease." In Western countries, patients have periods of stable weight interspersed with episodes of rapid wasting that often occur during active secondary infection. Over time, the recovery from bouts of wasting is less complete, producing long-term loss of body cell mass *(99)*.

Patients with the HIV muscle-wasting syndrome commonly have severe fatigue and proximal and distal limb muscle atrophy. On biopsy, these patients demonstrate diffuse or type II muscle fiber atrophy or mild neurogenic features as usually found in cachectic myopathy *(98)*. Proposed mechanisms for the development of the HIV muscle-wasting syndrome include elevated cachectin levels, cytokine effects on lipid metabolism, the development of anorexia and cachexia, and other metabolic disturbances *(99)*. Treatment of the HIV muscle-wasting syndrome consists of searching for and treating secondary infections, antiretroviral therapy, and nutritional supplementations *(99)*.

Several other types of myopathies have been reported in HIV-infected individuals, including a necrotizing, noninflammatory myopathy, nemaline (rod) myopathy, rhabdomyolysis, and myositis ossificans *(2)*. Finally, myalgia is a frequent symptom of acute HIV infection *(2)*, and fibromyalgia-like symptoms have been reported in 11–29% of consecutive unselected HIV-infected patients *(100,101)*. Cocaine use is also a common cause of creatine kinase elevation in outpatients infected with HIV *(102)*.

Vasculitis

Several different types of vasculitis have been associated with HIV infection (*see* Table 4) *(2,103)*. An autopsy study conducted on 148 symptomatic HIV-infected adult patients in Bobigny, France found that 34 patients (23%) had evidence of inflammatory vascular disease. Eleven patients (7%) could be classified has having a distinct category of vasculitis, including polyarteritis nodosa (4 patients), Henoch-Schönlein purpura (1 patient), and drug-induced hypersensitivity

Table 4
Vasculitides Associated with HIV Infection

Necrotizing vasculitis *(103,211–218)*
Leukocytoclastic vasculitis *(103,110,217, 219–222)*
Cutaneous polyarteritis nodosa *(223)*
Necrotizing folliculitis *(224)*
Eosinophilic vasculitis *(225,226)*
Churg-Strauss vasculitis *(108)*
Henoch-Schönlein purpura *(103,111,217)*
Isolated angiitis of the CNS *(103,227)*
Behçet's syndrome *(13,228,229)*
Relapsing polychondritis *(230)*
Erythema nodosum *(231)*
Cryoglobulinemia *(45,232–234)*
Zidovudine-induceld leukocytoclastic vasculitis *(109)*
CMV–induced vasculitis *(105,106,235–238)*
Herpes zoster-induced vasculitis *(239–241)*
Toxoplasma–induced vasculitis *(242)*
P. carinii-induced vasculitis *(243,244)*
Angiocentric immunoproliferative disorders *(103,112,245)*
Benign lymphocytic angiitis *(103,112)*
Lymphomatoid granulomatosis *(103,112, 163,246,248)*
Angiocentric lymphoma *(103,112)*

vasculitis (6 patients), and 23 patients were classified in the group "other vasculitis, type unspecified." Unlike vasculitic syndromes associated with infections, such as hepatitis B, which represent well-defined clinical entities, the vasculitic conditions associated with HIV infection represent a microcosm of the entire vasculitic spectrum *(103)*.

Polyarteritis Nodosa-Like Syndromes

At least 13 HIV-infected patients have been described with a polyarteritis nodosa-like syndrome *(104)*. These patients presented primarily with peripheral neuropathies, including symmetric sensorimotor neuropathies and mononeuritis multiplex. Digital ischemia with frank gangrene, other skin lesions, and evidence of gastrointestinal involvement on rectal biopsy have also been noted. Hepatitis B surface antigen was not detected in five HIV-infected individuals with polyarteritis nodosa-like syndromes who were tested for this antigen *(2,103)*.

Pathologically, the patients with HIV-associated polyarteritis nodosa-like syndromes resemble typical polyarteritis nodosa with necrotizing vasculitic lesions of medium-sized vessels. These histologic

findings have been most commonly demonstrated in small muscular arteries within muscles, as well as epineural arteries and arterioles. The infiltrates generally have been acute *(103)*.

HIV-associated polyarteritis nodosa-like syndromes are usually treated with prednisone in doses of 40–60 mg daily. Such vasculitic syndromes usually respond well to oral corticosteroids. Cytotoxic drugs, such as cyclophosphamide and azathioprine, should be avoided whenever possible because of the risk that these drugs will induce opportunistic infections.

It is not known if the necrotizing vasculitis in HIV-infected patients is a direct result of the HIV virus or not. Other viruses, such as hepatitis B and cytomegalovirus have been implicated in the pathogenesis of necrotizing vasculitis. In some cases, these viruses may be a factor in the pathogenesis of vasculitis in HIV-infected patients *(2)*. Three patients with AIDS who had cytomegalovirus-induced necrotizing vasculitis have been described *(105,106)*. On the other hand, HIV antigens may be involved in the formation of antigen–antibody complexes causing vasculitis in a manner similar to that of hepatitis B surface antigen. Immunofluorescent studies performed in two cases of leukocytoclastic vasculitis occurring in HIV-infected individuals gave some indication of such immune complex mechanisms *(103)*. The HIV virus may also have a direct effect on the blood vessel wall, thus causing vasculitis in some as yet unknown way *(2)*. Calabrese et al. *(107)* cultured HIV from peripheral nerves of an HIV-infected patient with necrotizing vasculitis, but could not demonstrate HIV in the vasculitic infiltrates.

A single case of allergic granulomatosis or Churg-Strauss syndrome in an HIV-infected patient has been described. The patient's physicians treated him with high-dose prednisone alone with an apparently good clinical response at 1 mo *(108)*.

Hypersensitivity Vasculitis

Several reports of small-vessel vasculitis in HIV-infected patients, often referred to as the hypersensitivity vasculitides, have been noted in the medical literature. A variety of viral infections often associated with HIV infections, including cytomegalovirus, Epstein-Barr virus, and hepatitis B are known to cause leukocytoclastic vasculitis. Cytomegalovirus has been linked with hypersensitivity vasculitis in HIV-infected patients. Other well-studied cases of small-vessel vasculitis have revealed none of the known causes of this type of vasculitis *(103)*. Zidovudine has been demonstrated to induce leukocytoclastic vasculitis in at least one case *(109)*. Henoch-Schönlein purpura has been reported in both adults and children infected with HIV *(103,110,111)*. No specific therapy is usually needed in these cases.

Primary Angiitis of the Central Nervous System

Primary angiitis of the central nervous system is an extremely rare disorder. Six of the 108 cases reported in the English literature through January 1990 have been in HIV-infected individuals *(103)*. Fulminant central nervous system symptoms occur, with histology revealing granulomatous involvement of cerebral arteries. Systemic necrotizing vasculitic symptoms, such as skin lesions, abdominal pain, foot and wrist drop, hematuria, and proteinuria, are absent. Histology reveals granulomatous involvement of cerebral arteries.

A combination of cyclophosphamide and corticosteroids is usually necessary to treat primary angiitis of the central nervous system in HIV-uninfected patients. Because of the severe immunosuppressive effects of cyclophosphamide and corticosteroids, such a treatment regimen cannot be recommended for HIV-infected individuals with primary angiitis of the central nervous system. Thus, there is really no good therapy for this unusual complication of HIV.

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis, part of a spectrum of disorders known as angiocentric immunoproliferative lesions, is a vasculitic disorder that often progresses to become angiocentric lymphoma. There have been at least six reports of this condition in HIV-infected individuals. Lymphomatoid granulomatosis development in the HIV-infected individual suggests that HIV-induced immune disregulation may at times lead to uncontrolled lymphoproliferation of T-cell lineages with an angiocentric predisposition. This T-cell proliferation contrasts with the vast majority of lymphomatoid neoplasms in HIV infection, which originate in the B-cell lines *(103,112)*.

In cases of lymphomatoid granulomatosis in HIV-infected individuals, the central nervous system has been the primary site of involvement of the vasculitis, although muscle, peripheral nerve, heart, lung, and kidney have also been affected *(103,112)*.

Therapy

No controlled trials of treatment of vasculitis in HIV-infected individuals has been undertaken. Each case of vasculitis needs to been treated individually. Certainly, high-dose corticosteroid, such as prednisone, 60–80 mg daily, should be employed in patients with potentially life-threatening disease. The use of cytotoxic drugs, such as cyclophosphamide, should be employed with caution because of the high risk of developing opportunistic infections.

Physicians at the Cleveland Clinic use combination chemotherapy for HIV-associated lymphoproliferative diseases with the patients who have an absolute CD4-positive cell count of 400–500 cells/mm^3. They

also put these patients on aggressive prophylaxis for opportunistic infections, including monthly iv immunoglobulin, monthly aerosolized pentamidine for *Pneumocystis carinii* prophylaxis, and daily acyclovir for viral prophylaxis *(103)*.

Sicca Syndrome

Clinical Features

Several authors have described patients with generalized lymphadenopathy and the sicca syndrome (xerophthalmia and xerostomia) in HIV-infected individuals. These patients have many clinical features in common with Sjögren's syndrome: clinically having dry eyes, dry mouth, parotid gland enlargement, and lymphadenopathy *(113–115)*. However, many important differences exist between HIV-associated generalized lymphadenopathy and sicca syndrome, termed diffuse infiltrative lymphadenopathy syndrome (DILS), and idiopathic Sjögren's syndrome. In contrast to idiopathic Sjögren's syndrome, DILS is frequently associated with extraglandular manifestations, such as lymphocytic interstitial pneumonitis, and lymphocytic infiltration of the gastrointestinal, neurologic, and reticuloendothelial systems. Parotid gland involvement in DILS, in contrast to idiopathic Sjögren's syndrome, is often massive, as is the degree of lymphadenopathy. Furthermore, the phenotype of the infiltrative lymphocytes in DILS is CD8, where as in Sjögren's syndrome, it is CD4. Furthermore, autoantibodies, such as rheumatoid factor, antinuclear antibodies, anti-Ro/SS-A, and anti-La/SS-B, which are commonly seen in idiopathic Sjögren's syndrome, are absent in DILS. The HLA association with idiopathic Sjögren's syndrome is B8, DR2, DR3, and DR4 (when associated with rheumatoid arthritis). In contrast, HLA-DR5 is associated with Black patients with DILS, and HLA-DR6 and DR7 are associated with White patients with DILS. Finally, HIV antibodies, found in all DILS patients, are absent in idiopathic Sjögren's syndrome *(113,114,116)*.

The clinical course in DILS is quite atypical for HIV-infected patients. Itescu et al. *(113)* at New York University followed 25 patients with DILS for a total of 822 patient-mo (range of follow-up, 12–144 mo), and only one patient has developed an opportunistic infection. Two patients died, one as a result of pneumococcal pneumonia complicating severe lymphocytic interstitial pneumonitis, and a second as a result of unrelated head trauma.

Therapy

The most common symptoms in DILS relate to salivary gland infiltration, with ensuing facial pain and discomfort; sicca symptoms; and recurrent sinus, middle ear, and oral cavity infections. Therapy with

antibiotics appropriate to the culture and infection site is usually effective for these problems.

Zidovudine may be helpful in diminishing salivary gland enlargement in many patients. Dosages of 250 mg orally four times a day may lead to symptomatic responses as early as 1 wk after starting zidovudine, with maximal benefits usually occurring after 6 wk. In general, discontinuation of zidovudine has resulted in rapid re-enlargement of the parotid glands. Artificial tears can be used for dry eyes. Chewing sugarless gum or sucking on sugarless candy may increase saliva production. Proper dental care is also essential in patients with DILS, since the lack of saliva leads to more frequent dental caries *(113,114)*.

Progressive pulmonary, gastrointestinal, and/or renal lymphocytic infiltration need to be further evaluated before instituting immunosuppressive therapy *(113)*. Tissue confirmation, either by transbronchial or open lung biopsy, of pulmonary lymphocytic infiltration as well as the use of gallium scans and pulmonary function tests can aid in the evaluation of pulmonary status in DILS patients. Lymphocytic infiltration of the kidneys, which can be manifest either by interstitial nephritis or renal tubular infiltration, may present with progressive renal insufficiency, hyperkalemia, and type IV renal tubular acidosis *(113,114)*.

If the pulmonary or renal disease in DILS progresses and is symptomatic, Itescu et al. *(113,114)* advocated treating with 40–60 mg of prednisone daily or with other immunosuppressive agents, such as chlorambucil, for 8–12 wk, unless the patient has a high degree of circulating HIV antigen load as assessed by p24 antigen levels. Patients are treated with zidovudine in addition to prednisone. Although typical side effects of high dose corticosteroid, such as weight gain, hypertension, hyperglycemia, and oral candidiasis, may be seen in patients with DILS, opportunistic infections have not been noted.

Autoimmune Phenomena

Various autoimmune phenomena have been reported in HIV-infected patients (*see* Table 5). The prevalence of these autoantibodies varies greatly been clinical series *(2,117)*. Two types of 35 autoantibodies, antiphospholipid antibodies and antinuclear antibodies, may-have special clinical and therapeutic significance.

Several studies have noted a markedly increased prevalence of antiphospholipid antibodies (anticardiolipin antibodies and the lupus anticoagulant in HIV-infected individuals *(4,10,117–130)*. In patients with rheumatologic diseases, such as systemic lupus erythematosus (SLE), antiphospholipid antibodies are associated with thrombotic events, like strokes and deep venous thromboses. There is no, such asso-

Table 5
Autoimmune Phenomena Associated with HIV Infection

Antinuclear antibodies *(4,117,134,249–253)*
Antiplatelet antibodies *(254–260)*
Antilymphocyte antibodies *(261,262)*
Antigranulocyte antibodies *(263,264)*
Direct antiglobulin (Coombs') test *(265–268)*
Antiphospholipid antibodies
Lupus anticoagulant *(118–122)*
Anticardiolipin antibodies *(4,120,122–129,269)*
Antineutrophil cytoplasmic antibodies *(253,270–273)*
Circulating immune complexes *(252,274)*
Rheumatoid factor *(117,274)*
Cryoglobulins *(232–234)*

ciation in HIV-infected individuals, since there have been only three reported cases of thrombotic events in HIV-infected patients with antiphospholipid antibodies *(131–133)*, and thus there is no need for routine anticoagulant therapy in these patients *(2)*.

Patients with the lupus anticoagulant, found in about 45% of patients with AIDS *(2)*, often have prolonged partial thromboplastin times. The prolonged partial thromboplastin time cannot be corrected by mixing the patient's serum with normal serum as can be done in hemophilia and other deficiencies of coagulation factors. Furthermore, the lupus anticoagulant is not associated with clinical bleeding problems. Thus, HIV-infected patients who are about to undergo an invasive procedure and have a prolonged partial thromboplastin time, should be evaluated for the presence of the lupus anticoagulant, rather than be denied a necessary procedure because of a perceived risk of bleeding *(118)*.

HIV infection and SLE share a number of clinical features in common (*see* Table 6). Antinuclear antibodies have been reported in up to 13% of HIV-infected patients *(134)*, although many other authors have not found antinuclear antibodies in the presence of HIV infection *(2)*. When a patient has the clinical symptoms outlined in Table 6 and a positive antinuclear antibody test, the diagnosis of SLE is often entertained, and treatment with corticosteroid, antimalarial drugs, and even cytotoxic agents may be considered. The principal difference between HIV infection and SLE is that there is laboratory evidence of HIV infection in the former, and not the latter. Although up to 10% patients with SLE may have antibodies to HIV detected by enzyme-linked immunosorbent assay (ELISA) method *(135)*, false-positive tests in lupus patients are extremely rare when western blot is employed *(136–138)*.

Table 6
Similarities Between Systemic Lupus Erythematosus and HIV Infection

Skin
Malar rash (from seborrhaeic dermatitis)
Joint
Arthritis and arthralgias
Oral ulcers
Kidney
Proteinuria
Blood
Thrombocytopenia
Leukopenia
Lymphopenia
Neutropenia
Coombs' positive hemolytic anemia
Nervous system
Seizures
Headaches
Dementia
Mononeuritis multiplex
Peripheral and cranial neuropathies
Myositis
Vasculitis
Sicca syndrome
Constitutional
Fever
Lymphad enopathy
Weight loss
Laboratory
Antiphospholipid antibodies
Antinuclear antibodies

There are only eight case reports of SLE occurring in HIV-infected individuals *(45,139–143)*. The reasons for the lack of association between HIV infection and SLE are not fully known. One possibility is epidemiologic; SLE occurs primarily in women, whereas in Western countries, HIV mostly afflicts men *(2)*. Second, the resulting immunologic abnormalities from HIV infection may attenuate the clinical manifestations of SLE, thus making the disease less obvious. In two documented cases, patients with SLE improved with concomitant lymphocyte depletion from the HIV infection. One patient was treated with zidovudine with a subsequent increase in the number of T-lymphocytes. At the same time, arthritis and pleuritis reappeared and anti-DNA antibody levels increased *(2,45,143)*. Finally, the marked antibody production in patients with SLE may somehow protect the patient from either devel-

oping HIV infection or expressing the immunodeficiency caused by HIV *(2)*.

Because of the risk of further immunosuppression, cytotoxic such drugs as azathioprine, methotrexate, and cyclophosphamide, should not be used in the treatment of HIV-infected patients with SLE *(2,8,15,20,23)*.

Drugs commonly used to treat rheumatic diseases, such as hydroxychloroquine, chloroquine, and *d*-penicillamine, have shown promise in inhibiting the replication of the HIV virus *(144–147)*.

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HIV and Psoriasis

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Introduction

Infection with the human immunodeficiency virus (HIV) may be complicated by psoriasis and/or an inflammatory arthritis. The clinical features of the arthritis are variable, and may resemble psoriatic arthritis or Reiter's syndrome *(1,2)*. The fact that both psoriasis and Reiter's syndrome may present for the first time or be exacerbated by HIV infection suggests that HIV infection enhances or triggers the expression of these diseases in a susceptible individual *(1,3)*. These diseases show significant etiological, clinical, and histological overlap, and are considered to be part of the same disease spectrum *(2)*.

Epidemiology

In one of the most definitive studies to date, Garbe et al. *(4)* followed a cohort of 456 HIV-infected individuals from 1982–1992. During this 10-yr period, psoriasis occurred in 6.4%. This figure is much higher than the prevalence of 2% found in the general population. A study undertaken by Berman et al. *(5)* reported a similar figure of 5%.

Researchers at the San Francisco General Hospital *(3)* found that one-third of HIV-infected patients with psoriasis developed psoriasis prior to HIV infection, whereas two-thirds noted the onset of psoriatic symptoms following seroconversion. The prevalence of 6.4% correlates well with this data. If one-third develops psoriasis before HIV infection, then the prevalence figure for this subgroup will reflect that of the general population, i.e., 2%. If two-thirds develop psoriasis after seroconversion, then the prevalence for this subgroup will be double that associated with the general population, i.e., 4%. When combining

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the prevalence figures for both subgroups, the overall prevalence for HIV-associated psoriasis would be expected to be approx 6%. Others *(6,7)* have, however, reported prevalences of 1.3–2%, similar to the general population.

The prevalence figures for psoriatic arthritis in HIV-infected individuals also vary. Berman et al. *(5)* and Solinger and Hess *(8)* reported prevalences of 2 and 1.2%, respectively. Psoriatic arthritis occurs in 5–10% of non-HIV-infected individuals with psoriasis and 0.05–0.14% of the general population. These two studies suggest that the prevalence of psoriatic arthritis is higher in the HIV-infected population. No study has demonstrated a correlation between the severity of the psoriatic skin lesions and the prevalence of arthritis in HIV-infected persons *(1)*.

Controversy also exists over the prevalence of Reiter's syndrome in the HIV-infected population, particularly since the prevalence in the general population has not yet been firmly established. Reported prevalences have ranged from a high of 5–10% *(5,9)* to a low of 0.3–0.5% *(10,11)*. This figure is similar to the prevalence in non-HIV-infected homosexual men, but much higher than the reported prevalence in the general population of 0.0035–0.004% *(12,13)*. These differences may relate to different rates of exposure to infectious agents known to trigger Reiter's syndrome.

Twenty percent of persons with HIV-associated psoriasis have their presentation with a CD^{4+} count >400 *(3,4)*. Approximately half of cases present before clinical findings of immunodeficiency (except for low CD^{4+} count) *(3,4)*. Therefore, both psoriasis and Reiter's syndrome may be the initial clinical manifestation of HIV infection.

Etiology

Although the etiology of psoriasis remains unclear, a multifactorial pattern has emerged with certain etiological factors having a strong association with both psoriasis and Reiter's syndrome. In particular both diseases have a strong genetic component and may be precipitated by infectious agents and certain drugs. These etiological factors remain true regardless of the HIV status of the individual, and the bulk of the evidence so far strongly suggests that psoriasis is the same disease in both groups.

Association with class 1 HLA antigens is well recognized. Although the frequency of HLA antigens in HIV-associated Reiter's syndrome is well established, little is known about the frequency of HLA antigens in HIV-associated psoriasis or psoriatic arthritis.

Reiter's syndrome is associated with HLA B27 in 80% of HIV-negative individuals, and a similar value of 70–80% has been found in HIV-

infected individuals *(2,5,14)*. This marked association strongly suggests a genetic predisposition.

Reveille et al. *(2)* examined the HLA antigen frequencies in HIV-infected male patients with psoriasis and psoriatic arthritis compared with noninfected controls. HLA B27 was found in 45% of all patients with psoriasis, including those with arthritis compared with only 6% in the control group. Those with psoriatic arthritis were found to have HLA B27 in 78% of cases, whereas only 23% of patients with psoriasis alone were found to have this particular antigen. Twenty-three percent of the patients with psoriasis alone expressed HLA B17, a figure that is three times higher than the 6% found in the control group, and 61% were found to have one or more B7 "CREG" antigens. Although these figures suggest a marked increase in HLA frequency, particularly HLA B27 and B17, the results did not attain statistical significance owing to insufficient sample size *(2)*.

Another important etiological aspect of Reiter's syndrome and psoriasis is the role played by infectious agents. The fact that Reiter's syndrome may be precipitated by a gastrointestinal or genitourinary-urinary infection has been well established. The definition of reactive arthritis is based on the temporal relationship between an infection distant to the joint and the subsequent development of arthritis. HIV-infected individuals are at increased risk of acquiring a range of bacterial, viral, and fungal infections, including recognized arithrogenic organisms, such as:

1. Shigella;
2. Salmonella;
3. Campylobactor; and
4. Chlamydia trachomatis.

Certain studies have identified a pathogen in 30% of HIV-positive Reiter's patients *(9)*. A higher than expected frequency of *Yersinia*-induced Reiter's syndrome in HIV-positive individuals has been reported in the UK *(15)*. Low chlamydia anybody titers in 60% and high chlamydia anybody titers in 33% of HIV-positive subjects compared with 8 and 1.7%, respectively, in HIV-negative healthy subjects have also been reported *(16)*.

Bacterial, fungal, and viral agents have all been implicated as trigger factors in the onset or exacerbation of psoriasis. Guttate psoriasis is frequently precipitated by streptococcal infection perhaps triggered by a streptococcal "superantigen" *(17)*. Patients with this form of psoriasis improve following treatment with systemic antibiotic therapy. HIV-associated guttate psoriasis may also show a dramatic response to antibiotic therapy. Some *Staphylococcus aureus* toxins can also act as "superantigens" *(18)*, and staphylococcal sepsis has been linked with

psoriatic flares in HIV-infected individuals *(19)*. However, whether the infection triggers the psoriatic flare or whether septicaemia follows the secondary infection of psoriatic plaques remains unclear *(19)*. Regardless of the specific initiating event, the resolution of psoriasis following iv antibiotic therapy is well documented *(19)*. A psoriatic flare in an HIV-infected individual should always raise the possibility of an occult staphylococcal infection even if the patient does not appear to be particularly unwell.

Drugs are also known to trigger or exacerbate psoriasis in both HIV-negative and HIV-positive individuals. Drugs identified in HIV-infected psoriatics as having a triggering effect include lithium, β-blockers, and systemic corticosteroids. Corticosteroid withdrawal following treatment of *Pneumocysts carinii* pneumonia or as a part of chemotherapy premedication for treatment of Kaposi's sarcoma has caused flares of psoriasis in patients followed by the authors. Removal of the corticosteroids as a part of the chemotherapy resulted in improvement of the psoriasis.

Pathogenesis

The advent of HIV infection and its recognized association with psoriasis and Reiter's syndrome has shed some light on the pathogenesis of these two closely related diseases. Does HIV infection have a unique role, or does it facilitate the pathogenic mechanisms that occur in non-HIV-infected individuals? The bulk of the evidence to date strongly supports the latter interpretation. The histological findings and etiological factors associated with psoriasis remain consistent regardless of the HIV status of the individual. Psoriasis is therefore considered to be the same disease in both HIV-negative and HIV-positive individuals, and the same pathogenic model for psoriasis can be applied to both groups.

Why is psoriasis more prevalent in HIV-positive individuals, and why does it tend to follow a more aggressive course? The CD^{4+} lymphocyte targeting by HIV results in the progressive depletion of CD^{4+} cells. The removal of such downregulating agents probably facilitates a variety of pathogenic mechanisms, which are no longer held in check Many unrelated conditions, for example, seborrhoeic dermatitis and pruritic folliculitis, are known to occur more frequently in HIV-infected individuals. No unifying process has been linked with this diverse list of diseases other than a reduced CD^{4+} count and a relative increase in CD^{8+} cells.

Attention has therefore become focused on the pathogenic effects of the progressive CD^{4+}/CD^{8+} imbalance and the possible direct effects of HIV itself. However, the possibility that CD^{4+} cells may have an active

role cannot be discounted, since several patients with end-stage AIDS and extremely low CD^{4+} counts have been noted to have a spontaneous remission *(20)*.

A Primary Immune Mechanism

The immunohistochemical characteristics of psoriatic lesions include the preferential localization of CD^{4+} lymphocytes in the dermis and CD^{8+} lymphocytes in the epidermis *(21)*. It has also been shown that the onset and exacerbation of psoriatic lesions are linked to the accumulation of CD^{8+} lymphocytes in affected areas, whereas remission following treatment is associated with a decrease in CD^{8+} lymphocytes *(22,23)*. An expansion of CD^{8+} cells could be induced by interleukin-2 (IL-2), released by HIV-infected lymphocytes. The activated CD^{8+} lymphocytes may then infiltrate the epidermis with subsequent keratinocyte activation and proliferation. HIV infection may set the stage for this postulated CD^{8+}-mediated process through the HIV-associated reduction in CD^{4+} count and relative increase in CD^{8+} count.

HIV and Arthritogenic Organisms

This theory is based on the increased incidence of opportunistic infections associated with HIV infection that may act as arithrogenic pathogens. In addition, a reduced immune reaction and response to infecting organisms was seen in HLA B27- and B7-positive individuals who developed a reactive arthritis following a salmonella epidemic *(24)*. The HIV-associated immunodeficiency may compound such an immune defect, as well as facilitating the emergence of opportunistic and potentially arthritogenic pathogens.

A Direct Role for HIV Involving Epidermal Langerhans Cells and Dermal Dendrocytes

In HIV infection and in psoriasis, epidermal Langerhans cells (ELC) are reduced *(25)*. In HIV-infected persons with psoriasis, this reduction is more marked *(25)*. It is unknown if this reduction of ELC in HIV-infected patients is owing to infection of ELC by HIV. What pathogenic role this reduction of ELC may play in psoriasis and whether the enhanced reduction of ELC associated with HIV disease is related to the increased severity of psoriasis in some HIV-infected patients are unknown.

Psoriatic lesions are associated with increased numbers of dermal dendrocytes *(26)*. Dermal dendrocytes are potential targets for HIV infection because they express CD^{4+} receptors and can function as phagocytes. Using *in situ* hybridization with nonfocal laser scanning microscopy, HIV transcripts have been demonstrated within the der-

mal dendrocytes of psoriatic lesions of HIV-positive individuals, but not in normal skin from HIV-positive patients or from the skin biopsies of seronegative psoriatic patients *(27)*. The finding of HIV-1 RNA sequences in the psoriatic lesions and not in the normal skin suggests that HIV may play a local role in triggering psoriatic lesions. The exact mechanism by which this may occur is unknown, but HIV itself directly triggering keratinocyte proliferation, or HIV-infected dermal dendrocytes stimulating keratinocyte proliferation indirectly through cytokine production has been proposed *(27)*. However, the role of dermal dendrocytes in HIV-associated psoriasis is not clear-cut. Although the density of dermal dendrocytes is increased in the psoriatic lesions of both HIV-positive and HIV-negative individuals, there is no significant difference in density between the two groups *(26)*. Therefore, the sudden onset or worsening of psoriatic lesions associated with HIV infection cannot be attributed to HIV-induced dermal dendrocyte proliferation. However, the results do not exclude a qualitative or functional abnormality.

HIV May Have a Direct Effect on Keratinocytes

Evidence for a direct role for HIV is provided by transgenic mice studies. In one study, the entire HIV proviral genome was inserted into mouse embryos. Forty-five percent of the offspring of one of these mice developed a syndrome with skin lesions that resembled psoriasis, suggesting that the HIV genome may drive epithelial proliferation *(28)*. It has been noted that some psoriatic HIV-positive patients receiving zidovudine (AZT) show marked and dramatic remission of their skin lesions *(29)*. More recently, AZT has been found to have a beneficial effect on the psoriatic skin lesions of HIV-negative individuals, although the benefit appears to be less dramatic than in HIV-positive individuals *(30)*. AZT is a thymidine analogue that inhibits viral reverse transcriptase. It also inhibits host DNA synthesis, so its effect on psoriasis may be explained by direct inhibition of keratinocyte proliferation by the drug itself *(20)*, a possibility supported by its therapeutic effect in HIV-negative psoriatic patients.

Bacterial Agents Acting as Triggers

S. aureus toxins have been shown to function as superantigens that interact with T-cells *(18)*. Once activated, the T-cells may induce a generalized psoriatic flare *(19)*, as observed in HIV-infected patients with *S. aureus* septicemia. In immunocompetent individuals, psoriatic lesions, although colonized, uncommonly become infected. By comparison, more than 50% of HIV-positive psoriatic patients have been found to have staphylococcal skin infections, in particular, folliculitis and intertriginous impetigo *(6)*. In addition, *Candida albicans* infections are increased in HIV-

infected patients, and there are reports of non-HIV-infected patients with chronic plaque psoriasis whose symptoms were exacerbated by cutaneous infections with superantigen-secreting *C. albicans (31).*

In summary, although it appears that HIV-associated psoriasis may occur owing to the imbalance of CD^{4+}/CD^{8+} cells caused by HIV infection, increased infections with arithrogenic pathogens, infection of cutaneous antigen-presenting cells (dermal dendrocytes and perhaps epidermal Langerhans cells) by HIV, a direct effect of HIV on epidermal proliferation, and increased rates of infection with agents that produce "superantigens" may all play a role. Most likely, during the course of HIV disease, some or all of these factors may exert an effect on the psoriasis of the HIV-infected person.

Clinical Features

The spectrum of psoriasis, psoriatic arthropathy, and Reiter's syndrome is broad with substantial clinical overlap, and the distinction between them on clinical grounds is often difficult. For instance, typical lesions of keratoderma blenorrhagica can occur in a patient with otherwise typical psoriasis in the absence of arthritis. Although the clinical manifestations of HIV-associated psoriasis are similar to those of non-HIV-infected individuals, there are some variations. Researchers at the University of California, San Francisco found that HIV-associated psoriasis falls into two main clinical groups *(3)*:

1. Group 1 (psoriasis begins before HIV seroconversion): The onset of symptoms precedes seroconversion and characteristically occurs in the second decade with a mean age of onset of 19 yr (range of 10–30 yr). There is often a positive family history of psoriasis. Although any pattern of psoriasis can occur in this group, the clinical features correspond to the classical psoriatic patterns seen in non-HIV-infected individuals, and are most commonly one of the following three patterns:
   a. Typical psoriasis vulgaris;
   b. Guttate psoriasis: a common pattern even in the absence of a preceding streptococcal infection;
   c. Erythrodermic psoriasis.
2. Group 2 (psoriasis begins after HIV seroconversion): The onset of psoriasis follows HIV seroconversion usually by about 5 yr. This group is older, with a mean age of psoriasis onset of 36 yr (range 23–58 yr). A family history of psoriasis is generally absent. The clinical features tend to differ from those associated with classical psoriasis. In particular, inverse psoriasis and involvement of the palms and soles are more common, and may be indistinguishable from Reiter's syndrome. The patterns of psoriasis observed in the group include:

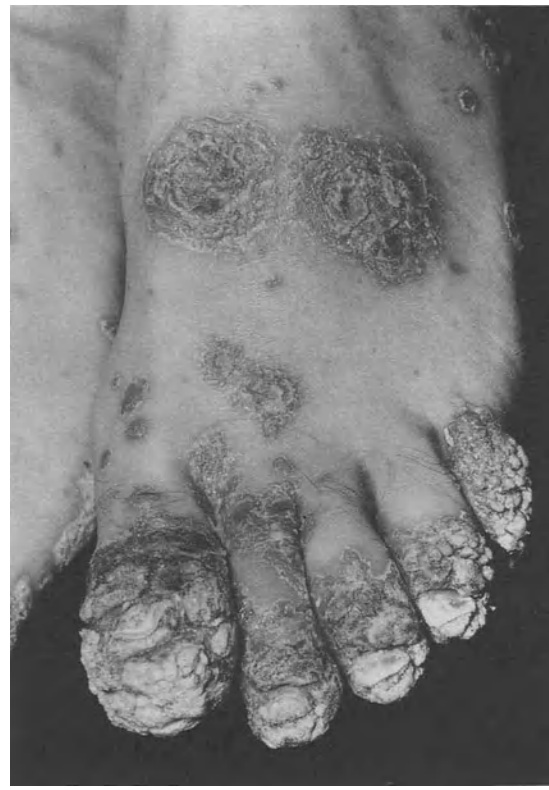

Fig. 1. Markedly hyperkeratotic plaques of the foot. These lesions resolved with low-dose etretinate (37.5 mg daily) and aggressive local measures (tar soaks, topical tar ointments, and quartz light treatments).

a. Psoriasis vulgaris;
b. Acral psoriasis with palmoplantar keratoderma (keratotic papules and pustules); Keratoderma blennorrhagicum (Fig. 1);
c. Inverse psoriasis with prominent plaques in the scalp, axillae, and groin (Fig. 2);
d. Pustular psoriasis; and
e. Erythrodermic psoriasis (may occur as frequently in this group as in group 1).

Multiple types of psoriatic lesions may occur simultaneously in the same patient *(3,6)*. The prevalence of psoriatic arthritis varies between the two groups, occurring with greater frequency in group 2 *(3)*.

Psoriasis may appear at any clinical stage of HIV disease, and the features may be mild, moderate, or severe *(3)*. Some researchers report that the severity of psoriasis tends to reflect the stage of HIV disease and often worsens as HIV disease progresses *(1)*. Not all studies have

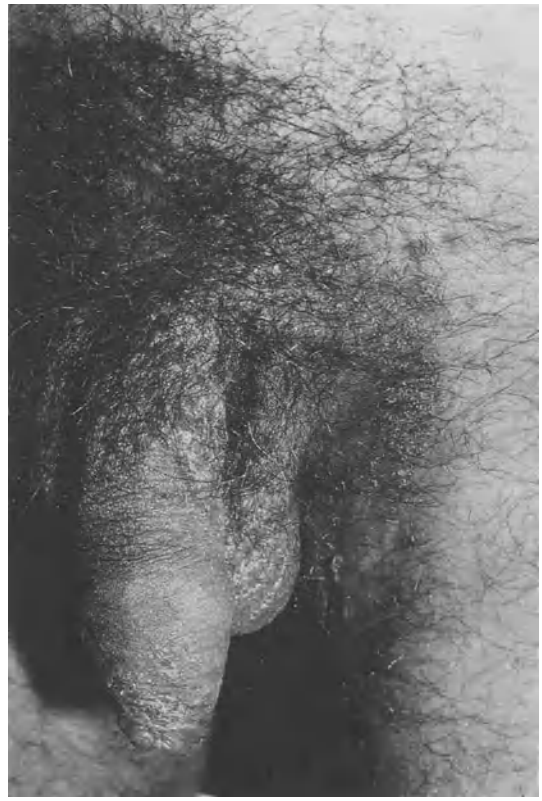

Fig. 2. Fixed, red, scaling plaque of the groin extending onto the scrotum and penis in a patient with Reiter's syndrome and AIDS.

detected such a direct correlation. Researchers in San Francisco found all grades of psoriasis in patients with a range of HIV disease *(3)*. However, either extreme of the HIV disease spectrum is often associated with a corresponding degree of skin involvement. Patients with asymptomatic HIV infection tend to have mild psoriasis and patients with low CD^{4+} counts generally have severe psoriasis *(3)*.

Factors known to exacerbate psoriasis in HIV-negative psoriatic patients may also worsen the skin lesions of HIV-infected individuals. These include infectious agents and certain drugs. The sudden flare of HIV-associated psoriasis may reflect an underlying staphylococcal infection even if the patient does not appear to be severely ill, and an occult infection must always be excluded *(19)*.

There are subtle histologic features that distinguish HIV-associated psoriasis from psoriasis in the seronegative. These include the presence of individually necrotic keratinocytes in the epidermis and plasma cells in the dermal infiltrate. These features are also seen in other

HIV-associated skin conditions, and are more reflective of the pattern of HIV-associated skin diseases than HIV-associated psoriasis in particular. As in psoriasis in the uninfected patient, if the clinical lesions are atypical, the histology is atypical. Clinically typical HIV-associated psoriasis usually has typical histologic features. We have found biopsies to be most useful at the onset of psoriasis, where small papules and plaques are not clinically typical, but usually histologically have sufficient features to allow us to diagnose psoriasis. Psoriasis does not appear to affect the survival of HIV-positive patients adversely *(3)*. However, studies so far have not been large enough to detect a significant difference.

The joint and tendon involvement in HIV-associated psoriasis and Reiter's syndrome tends to be more severe than in the general population and less responsive to anti-inflammatory drugs *(1)*. In addition, the number of joints affected tends to increase with time.

Psoriatic arthropathy in HIV disease is clinically identical to the joint involvement in immunocompetent psoriatics. It primarily affects the foot and ankle, and is often accompanied by intense enthesopathy and dactylitis, especially in the feet, which may be the major source of disability. The pattern of arthritis in both HIV-associated psoriatic arthritis and Reiter's syndromes as follows *(1)*:

1. Predominantly lower limb oligoarthritis;
2. Dactylitis;
3. Heel and foot enthesis;
4. Distal interphalangeal joint involvement; and
5. +/– Polyarthritis.

The radiological appearance of hands and feet in psoriatic arthritis often reveals classical psoriatic arthritis features with "pencil and cup" deformities and osteolysis *(32)*.

In summary, the clinical features of HIV-associated psoriasis and Reiter's syndrome are often modified by HIV infection, resulting in a shift in the presentation and natural history of these conditions.

Treatment

In treating an HIV-infected psoriatic, several simple management tips are often useful. First, look for secondary infection. Flares of HIV-associated psoriasis can be associated with skin infections. Often a course of antistaphylococcal antibiotics will improve HIV-infected psoriatics. Chronic antibiotic treatment and the control of nasal carriage may lead to improvement or stabilization of HIV-associated psoriasis. Even erythrodermic psoriasis may be the result of subclinical staphylococcal sepsis as noted above *(19)*. Blood cultures are in order in the HIV-infected patient with sudden development of psoriatic erythroderma.

Zidovudine can be added to the anti-HIV regimen of the patient. When used as sole treatment, AZT toxicity is often limiting. AZT in lower doses added to other antivirals is often well tolerated, and may have some benefit on the patient's psoriasis *(7,29,33)*.

The treatment of psoriasis in an HIV-infected individual can be difficult because many of the therapeutic modalities involve some degree of immunosuppression. The reduced range of options can pose a significant therapeutic challenge. The three-tiered treatment approach for standard psoriasis also applies to HIV-associated psoriasis with some modification.

The first level of treatment involves the application of topical agents, that are most effective in mild or localized disease. Topical steroids and calcipotriol can be prescribed as for any psoriatic patient *(34)*. Other alternatives in this group include anthralin (including short contact therapy) and tar preparations. The use of high-concentration tar products may be associated with folliculitis. Topical therapy requires high compliance for benefit. Unfortunately, in patients with advanced HIV infection, associated fatigue, depression, dementia, or the presence of multiple other medical requirements often prevent the regular application of topical medications. In the very ill patient, simple occlusion of lesions with semipermeable dressings is an effective alternative. Duoderm or similar dressings are applied to the affected areas and left on for a week at a time. Lesions tend to begin to fade in about 3 wk with no other management. Where occlusion is not an option, we are more likely to move to retinoid or phototherapy in the HIV-infected patient, recognizing the severe limitations of topical treatment in this setting This is especially true if the psoriasis is gradually worsening.

The intermediate treatment level covers the various forms of phototherapy. The indications include extensive involvement or severe localized psoriasis as in keratoderma blennorrhagicum. There is some debate concerning whether phototherapy is immunosuppressive and whether it may cause viral activation *(35)*. Although serum HIV titers may be transiently elevated by light therapy, the clinical importance of this finding is unclear. When looked at as a group, HIV-infected psoriatics treated with phototherapy do not seem clinically to suffer acceleration of their HIV disease *(35,36)*. Kaposi's sarcoma, however, does seem to be exacerbated by phototherapy, and KS is a relative contraindication to phototherapy.

In addition, HIV-infected individuals (more commonly those with dermatitis or folliculitis rather than psoriasis) are often more photosensitive. This may be related to HIV disease itself or the photosensitizing medications HIV-infected patients frequently require, for example, trimethoprim/sulfamethoxazole and the nonsteroidal anti-inflammatory agents. Our phototherapy unit has for these reasons modified

phototherapy in HIV-infected patients in the following ways. First, phototherapy is initiated and increased with caution. Initial dosing is begun at the level for one skin type less than the HIV patients actual skin type, i.e., the HIV-infected patient with type IV skin is begun as if his or her skin was type III. Patients are carefully observed for erythema, and frequent dose modifications may be required. Second, because of the concern about immunosuppression, patients receive phototherapy to only the areas required. We attempt local treatment, such as quartz light, more aggressively in HIV-infected patients. When the patients are treated in a light box, they expose only the targeted area. Patients may be treated on only half the body, for instance, if the psoriasis involves predominantly that area. The head and face are frequently shielded.

For the aforementioned reasons, standard outpatient phototherapy is more difficult in the HIV-infected patient. We have found, however, that retinoid therapy is well tolerated in general, and many patients are therefore begun on retinoids in low doses in anticipation of using phototherapy in the future. With low-dose etretinate treatment (25 mg daily), psoriasis may improve or stabilize. The combination of retinoids plus phototherapy allows less light to be used, and results in more rapid clearing of the psoriasis. Most patients with HIV-associated psoriasis in our center who get phototherapy receive RE-UVB. We have avoided PUVA because of theoretical concerns of immunosuppression. This is not based on actual data, but the fact that PUVA delivers light deeper into the skin, reaching the dermis where HIV-infected dermal dendrocytes have been demonstrated. Other centers have used PUVA without complications. Should PUVA be required, we would also recommend prior initiation of retinoids and the use of RE-PUVA for the reasons aforementioned. We have made regular use of topical PUVA for hand and foot psoriasis, in combination with oral retinoids, with success.

When outpatient phototherapy is ineffective, in the uninfected patient, we might proceed to methotrexate or cyclosporin A *(37,38)*. In the setting of HIV, because of our concern in the use of these immunosuppressives, we have favored the "Day Treatment" approach. Patients are admitted to the Day Treatment Center and given very intense Goeckerman or Ingram therapy. Patients with even the most recalcitrant disease tend to respond well to either regimen. With 3–4 wk of intensive treatment, very severe patients can be improved. In "Day Treatment," maximal use can be made of local therapies to target problem areas, usually the hands and feet. These patients are put into a remission that is maintained with oral retinoids and intermittent phototherapy, avoiding immunosuppressive agents. The disadvantage of this approach is its higher cost, but we believe this is warranted to

avoid the use of potentially life-threatening immunosuppressives in an already immunocompromised host.

The third level of treatment includes the oral agents. As mentioned, we begin retinoid therapy early, and use it aggressively in the HIV-infected patient with psoriasis. It has been of tremendous benefit, and toxicity has been minimal. This is because it seems to work at reasonably low doses in some HIV-infected patients. Many of our patients have hepatitis B and C virus infection, but liver function test abnormalities have only occasionally required us to discontinue retinoid therapy.

Cyclosporin and methotrexate are last-line agents, and we consider them relatively contraindicated on the basis that they theoretically could accelerate immunosuppression. However, there are case reports describing the beneficial use of both agents in HIV-associated psoriasis without significant worsening of HIV disease and we have used methotrexate when required in the photosensitive psoriatic intolerant or failing retinoid therapy *(37,38)*. In fact, an HIV-positive renal transplant patient has been described as receiving cyclosporin for 8 yr without experiencing adverse effects *(39)*. There are insufficient survival data to comment on the outcome of such treatment.

It appears that MTX and CSA are better tolerated early in HIV disease and are of greater risk in patients with advanced disease, when additional immunosuppression can lead to life-threatening opportunistic infections. If MTX or CSA is to be considered in an HIV-infected patient adequate prophylaxis for *Pneumocystis* pneumonia, mucosal candidiasis, cryptococcosis, *Mycobacterium* avium complex, herpes simplex, and perhaps cytomegalovirus and toxoplasmosis in the person seropositive for these latent agents should be considered. A high level of vigilance must be maintained for the development of one of these infections. These agents should be used as required, and once the psoriasis has improved, the dose reduced and attempts made to change to safer treatment. For instance, treat with MTX, and then switch to retinoid or RE-UVB for maintenance.

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Allergic Manifestations in AIDS

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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 persistently elevated IgE (14 of 19) compared to those with normal IgE levels (2

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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 $<300/\mu L$ 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 sug-

gest 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→ 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→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→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 Rhinosinusitus 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 fumigates* (6%), and *Staphylococcus aureus* (3%) *(32)*. Unusual pathogens have been reported in HIV-related chronic sinusitis, such as cytomegalovirus, *Enterobacter* sp., *Klebsiella pneumonias* 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/μL *(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 inspisated 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/μL) *(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 haptenated 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 *Pneumocyslis 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 P_{450} 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 N^4-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 P_{450} 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 exits, 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 haptenation 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 $<300/\mu L$ *(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/μL) 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 dentritic 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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Adverse Reactions to Trimethoprim-Sulfamethoxazole

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Clinical Description of Adverse Reactions to Trimethoprim-Sulfamethoxazole (TMP-SMX) in AIDS Patients

TMP-SMX is the drug of choice for the treatment and prophylaxis of *Pneumocystis carinii* pneumonia (PCP) in patients with the acquired immunodeficiency syndrome (AIDS). However, the therapeutic benefit of this drug combination is often limited by a high incidence of serious adverse reactions. An increased frequency of adverse reactions to TMP-SMX in HIV-infected patients has been noted *(1–5)*. Kovacs et al. *(1)* reported that 22 (65%) of 34 patients with AIDS developed adverse reactions while being treated with TMP-SMX, but only 2 (12%) of 17 patients without AIDS who were similarly treated had adverse responses. Jaffe et al. *(2)* noted that 8 (44%) of 18 patients treated with iv TMP-SMX developed fever, rash, and cytopenias; four patients were rechallenged, and all experienced a recurrence of their rashes. Gordin et al. *(3)* found that 83% of patients with AIDS developed one or more adverse reactions, and that in 65% of them, TMP-SMX had to be discontinued. Mitsuyasu et al. *(4)* reported cutaneous eruptions in 16 (64%) of 25 patients treated with TMP-SMX, including 8 of the 10 patients who received it only for prophylaxis. Medina et al. *(5)* found that 17 (57%) of 30 patients with AIDS developed major adverse reactions to TMP-SMX, and 29 (95%) of 30 patients developed minor adverse reactions. These adverse reactions typically include rash, nausea and vomiting, neutropenia, fever, thrombocytopenia, and hepatitis.

The most common adverse reaction involves a cutaneous rash. The majority of cutaneous reactions can generally be treated symptomatically with antihistamine medications; the rash in many cases will resolve without further sequelae, despite continuation of TMP-

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SMX. In addition, certain studies have found that a history of previous intolerance is not necessarily a contraindication to retreatment with TMP-SMX *(6)*. In a series of 21 patients with a history of rash while receiving iv TMP-SMX for treatment of acute PCP, Shafer et al. *(7)* found that only 4 had recurrence of the rash on rechallenge; in only 1 was the rash severe.

In contrast to cutaneous reactions to TMP-SMX, which occur frequently, the major systemic reactions seen in AIDS patients are apparently very rare. Kelly et al. *(8)* reported a series of 10 cases of severe systemic reactions in HIV-infected patients on rechallenge with TMP-SMX. In these patients, rechallenge with TMP-SMX after an average interval of 2–3 wk (range 5 d to 5 wk) resulted in a severe multisystem syndrome within 15 min to 5 h after rechallenge, consisting of high fever (>39°C), symptomatic hypotension, new pulmonary infiltrates, rash, and conjunctival infection; in many patients, acute elevation of serum creatinine, and/or serum transaminase and rhabdomyolysis were present as well. Patients experiencing this syndrome on rechallenge with TMP-SMX usually had a history of adverse reactions with the initial course of therapy, consisting of rash, fever, gastrointestinal intolerance, and/or leukopenia. However, in some patients, the original course of therapy had been completed without incident. Thus, from this series of 10 patients, the presence, absence, or character of previous adverse reactions did not predict ensuing severe reactions. However, a striking feature of this series is that the severe reactions generally occurred within the first 5 h of rechallenge with TMP-SMX.

Metabolic Basis of Sulfonamide Adverse Reactions: Role of Altered Drug Metabolism in AIDS Patients

Patients with AIDS have a higher incidence of adverse drug reactions than patients without AIDS particularly to TMP-SMX *(1–5)*. One possible explanation for this increased incidence is abnormal patterns of drug metabolism. Drugs, such as sulfonamides, dapsone, and isoniazid, that are commonly used in AIDS patients are metabolized in the liver by two metabolic pathways: oxidative metabolism by the cytochrome P-450 mixed-function oxidase, and *N*-acetylation mediated by *N*-acetyltransferase *(9–11)*. *N*-acetylation plays an important role in the biotransformation of drugs with arylamine or hydrazine groups, such as sulfonamides, dapsone, and isoniazid. The population ratio of rapid vs slow acetylators varies widely among ethnic groups throughout the world. With some exceptions, the clinical consequences of differences in acetylator phenotype are that slow acetylators develop more adverse reactions, whereas rapid acetylators are more prone to show an inadequate response to a standard dose.

We have asked whether altered patterns of drug metabolism in patients with AIDS might be a factor in the increased incidence of adverse reactions *(12)*. Using caffeine as a pharmacologic probe, we compared the activity of four enzymatic pathways for drug metabolism—acetylation (*N*-acetyltransferase), and three oxidative pathways, demethylation (cytochrome P 4501A2), xanthine oxidation (xanthine oxidase), and 8-hydroxylation—in three groups of HIV-infected patients and a control group. The groups were AIDS patients with acute illness, stable AIDS patients with a history of adverse reactions to TMP-SMX, HIV-infected patients without AIDS and healthy controls.

In the AIDS patients with acute illness, the prevalence of slow acetylation was greater than in the controls (27 of 29, or 93%, vs 18 of 29, or 62%) ($p < 0.01$). In addition, demethylation was decreased and 8-hydroxylation was increased in these patients. Xanthine oxidase activity was the same as in the controls.

In the AIDS patients who were stable, the activity of oxidative pathways was similarly altered as in the AIDS patients with acute illness. However, the prevalence of slow acetylation was the same as in the controls (66 and 62%, respectively).

In the HIV-infected patients without AIDS, the prevalence of slow acetylation (56%) and the activity of oxidative pathways were the same as in the controls.

These altered patterns of drug metabolism may be one reason for the increased incidence of adverse reactions to drugs in AIDS patients with acute illness. In other types of patients, slow acetylators have been shown to be prone to adverse reactions *(13,14)*. For example, slow acetylation is a risk factor for the development of a hypersensitivity reaction in children without AIDS treated with sulfonamides *(13)*. Similarly, in a group of dermatology patients receiving dapsone, patients who developed adverse drug reactions were slow acetylators, but had increased hydroxylation (as our patients did), despite having similar dapsone plasma levels to those in unaffected patients *(14)*. Since slow acetylation has been associated with increased risk of toxicity from a variety of drugs, including isoniazid, hydrazine, and procainamide as well as sulfonamides and dapsone *(13–15)*, slow acetylation in patients with AIDS who have acute illnesses may explain at least in part their increased risk of adverse reactions to drugs.

The cause of the increased prevalence of slow acetylation in acutely ill AIDS patients is not known. Our results suggest that it is not HIV infection *per se*, since only AIDS patients with acute illness had an increased prevalence of slow acetylation. Rather, the cause may be the acute illness. The acute illness associated with AIDS patients appears to reduce the ability of these patients to metabolize drugs, at least by some pathways.

A mechanism by which slow acetylation may lead to an increased incidence of adverse reactions to drugs has been proposed *(13,14,16,17)*. Because of the slow acetylation, more of the drug is shunted to the alternative oxidative pathways. These pathways form toxic metabolites (hydroxylamine and nitroso compounds), which are normally detoxified by scavengers, such as glutathione *(18,19)*. However, HIV-infected patients have low concentrations of glutathione *(20)*, so the toxic metabolites accumulate. The accumulated metabolites may then bind to macromolecules, causing cellular injury, and may be expressed clinically as an adverse reaction.

To support further our finding of slow acetylation, thus leading to an increase in the formation and accumulation of the toxic metabolite hydroxylamine, we found that in AIDS patients with PCP treated with TMP-SMX, the amount of SMX-hydroxylamine was significantly higher on d 10 of treatment than d 3 *(21)*.

The percentage of SMX-hydroxylamine excreted on d 3 in our patients was comparable to that published by Cribb and Spielberg *(19)*. Unexpectedly, in our patients, the amount of SMX-hydroxylamine excreted by d 10 was double that of those found on d 3. This increase in the amount of SMX-hydroxylamine excreted on d 10 suggests that there may be either an increase in the formation or a decrease in the detoxification of the hydroxylamine metabolite over time.

One possible explanation for decreased demethylation in AIDS patients may be the increased production of interferon found during viral infections. Interferons have been shown to decrease drug metabolism during viral infections, as a result of increased production of interferon and subsequent inhibition of cytochrome-P450 synthesis *(22,23)*. Decreased metabolism of theophylline, another drug metabolized by cytochrome-P 4501A2, an enzyme responsible for demethylation, has been reported in children during viral epidemics *(24–27)*.

Although xanthine oxidation was not significantly different among the three groups of patients and the control subjects, AIDS patients with acute illness tended to have increased xanthine oxidase activity. This increased activity may also be explained by increased production of interferon, since xanthine oxidase is induced by interferon *(22)*.

We found that the activity of 8-hydroxylation was increased in both groups of patients with AIDS. The cytochrome-P450 enzyme responsible for 8-hydroxylation has yet to be identified.

In summary, patients with AIDS have a high incidence of adverse reactions to TMP-SMX. We have found that the prevalence of slow acetylation is increased in AIDS patients who have acute illness and that the activity of the oxidative pathways is altered, demethylation being decreased and 8-hydroxylation increased. These altered patterns of drug metabolism may be one reason for the increased incidence of adverse reactions to drugs in AIDS patients with acute illness.

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