

Review article

Immunologic and clinical aspects of human immunodeficiency virus infection

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In 1981, a number of young male homosexuals in the USA became affected by an unusual association of diseases, such as *Pneumocystis carinii* pneumonia (PCP), Kaposi's sarcoma (KS), and systemic lymphadenopathy (10, 29, 50, 70). They were the first cases in the world of a new syndrome caused by a severe acquired immunodeficiency, which was therefore named acquired immunodeficiency syndrome (AIDS) (11). The cause of AIDS is a retrovirus belonging to the subfamily *Lentivirinae*, now known as human immunodeficiency virus (HIV) (6, 19, 64). Two different types of AIDS-causing viruses (HIV-1 and HIV-2) (6, 17) have been identified, but HIV-1 causes the great majority of AIDS cases registered so far throughout the world.

Although the course of HIV infection may vary markedly from case to case, a common form of progression is recognizable in all infected persons (Fig. 1) (57). The primary infection may be completely asymptomatic, but it is frequently characterized by viremia with or without an acute, mononucleosis-like syndrome (initial phase) (22, 38). This is followed in a few weeks or months by a humoral, cell-mediated immune response against the virus. As a consequence of this response, the virus disappears from the circulation, but colonizes in lymph nodes and other lymphoid tissues, where viral particles are trapped in the network of follicular dendritic cells (FDC) (57). Such an initial phase is followed by a

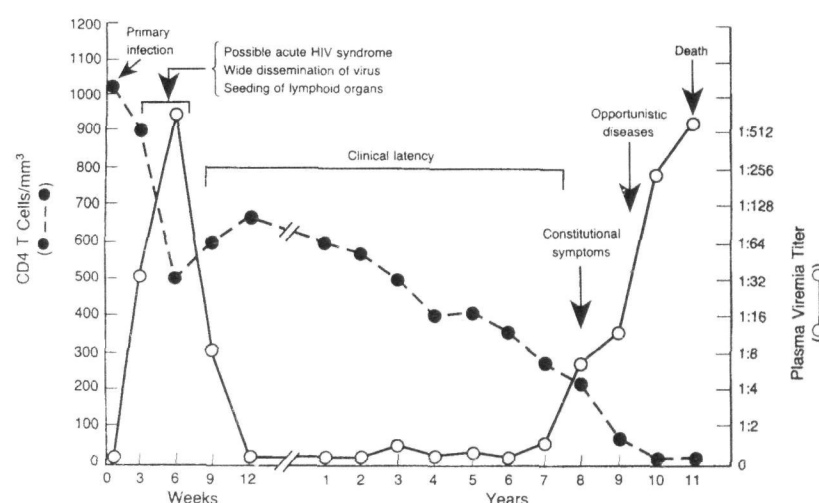


Fig. 1. Typical course of HIV infection. Peak of viremia and sharp decrease in number of CD4 + T cells in peripheral blood appear soon after infection (initial phase). HIV-specific response then ensues, with decrease in detectable viremia followed by prolonged period of clinical latency. CD4 + T-cell count continues to decrease during following years (intermediate phase) until dropping to critical level, below which there is substantial risk of development of full-blown disease (final phase) (from reference 58).

second phase of long clinical latency, lasting, on average, 7–10 years (intermediate phase). Recent studies, however, have clearly shown that, despite the lack of symptoms, virus replication occurs even during the phase of apparent clinical latency at the level of lymph nodes until the network of FDC is dissolved and node architecture completely disrupted (24, 58). During this phase, virtually all HIV-

infected patients show a gradual deterioration of the immune system, manifested particularly by the depletion of CD4 + T cells (57). At the end, viremia reappears, and HIV infection becomes clinically apparent either as severe and persistent constitutional signs and symptoms, or as an opportunistic infection or neoplasm (final or crisis phase), resulting in the death of HIV-infected subjects in about 1–2 years (Fig. 1) (57).

Immunopathogenic mechanisms

In HIV-infected subjects, several mechanisms probably contribute to the progressive deterioration of the immune system until its collapse which results in the development of full-blown disease (57). It is important to emphasize that hyperactivation and suppression of the immune response both coexist and alternate during the course of infection, the latter being prevalent in the final phase. Moreover, the function of both HIV-infected cells (CD4 + T cells and antigen-presenting cells (APC)), and uninfected cells (CD8 + T cells, B cells, and natural killer (NK) cells) of the immune system is altered. Finally, a series of complex abnormalities in the network of cytokines produced by APC, T cells, and effector cells occurs.

CD4 + T helper (Th) cell depletion and dysfunction

The question of what causes depletion and dysfunction of CD4 + Th cells in HIV infection has generated much debate and a plethora of explanations (Table 1). HIV can cause directly cytopathic effects in activated CD4 + T cells *in vitro*, either in single cells or by syncytium induction (21, 32). Single-cell killing may result from the accumulation of unintegrated viral DNA or from inhibition of cellular protein synthesis after HIV infection (21, 32). The formation of syncytia involves fusion of the cell

membrane of an infected cell with the cell membranes of uninfected CD4 + T cells, resulting in giant multinucleated cells (21, 32). A direct relation between the presence of syncytia and the degree of the cytopathic effect of the virus in individual cells has been observed *in vitro*, and HIV isolated during the accelerated phase of infection *in vivo* shows a greater capacity to induce syncytia *in vitro*. By incorporating noninfected cells into syncytia, a single HIV-replicating cell can eliminate many uninfected CD4 + cells, the so-called bystander effect. However, syncytia have rarely been observed *in vivo*; thus, their actual role in the genesis of CD4 + T-cell depletion remains unclear (21, 32).

Both humoral and cell-mediated immune responses against HIV may also contribute to CD4 + T-cell depletion and dysfunction. Antibodies directed against some regions of the envelope of HIV may mediate antibody-dependent cellular cytotoxicity (ADCC) after binding to NK cells, leading to the killing of HIV-infected CD4 + T cells which express viral-envelope proteins on their surfaces (26). HIV-expressing cells (CD4 + T cells, macrophages, and FDC) are also killed by HIV-specific, cytotoxic T cells, which are the normal mechanism for eliminating virus-infected cells by cell-mediated immunity (75). While this mechanism may play a protective role in the initial immune response to HIV infection, it becomes pathogenic in the chronic phase of infection and certainly contributes to the progressive deterioration of the immune system.

Because of the structural similarity between gp120 and gp41 proteins of HIV-1 and nonpolymorphic determinants of major-histocompatibility-complex (MHC) DR and DQ molecules, antibodies against these HIV proteins cross-reacting with MHC class II determinants may be produced (28). These antibodies may prevent interaction between CD4 expressed on the Th cell and class II molecules expressed on the APC, thus inhibiting the cellular interaction required for efficient antigen presentation, and impairing antigen-specific functions mediated by CD4 + Th cells (28). It has also been suggested that gp120 acts as an “alloepitope” (31); this means that gp120 bound to the CD4 molecules of T cells may trigger a long-term, allogeneic immune response. However, more convincing experimental evidence is required to substantiate these hypotheses.

There has been speculation that either anergy or programmed cell death (apoptosis) of CD4 + Th cells may also be induced by the binding of gp120 or complexes of gp120 antigen and antibody on the CD4 molecule (3). *In vitro*, CD4 + T cells incubated with gp120-anti-gp120 immune complexes become anergic to further *in vitro* stimulation through the activation of their CD3 molecules (55). Apoptosis is a normal mechanism of cell death that was originally

Table 1. Mechanisms thought to cause functional abnormalities and quantitative depletion of CD4+ T cells

Caused by HIV, its components, or both
– Directly HIV-mediated cytopathic effects (single-cell killing)
– HIV-mediated formation of syncytia
– Apoptosis induced by gp120 or gp120–anti-gp120 immune complexes
– Anergy induced by gp120 or gp120–anti-gp120 immune complexes
– Superantigen-mediated perturbation of T-cell subsets
– Infection of bone marrow or thymic precursors
– Alteration of T-cell homeostasis
Caused by immune response against HIV
– HIV-specific cytolytic T cells
– Antibody-dependent cellular cytotoxicity (ADCC)
– Natural killer (NK) cells
– Th1/Th2 switch
– Autoimmune mechanisms

described in the context of thymic maturation, whereby the body eliminates autoreactive clones of T cells. Because apoptosis can be induced in mature CD4⁺ T cells after CD4 molecules are cross-linked to one another and the T-cell antigen receptor (TCR) has been triggered, it has been suggested that cross-linking of the CD4 molecule by gp120 or gp120-anti-gp120 immune complexes prepares the cell for the apoptosis that occurs when the specific antigen in association with MHC class II determinants is presented to the TCR (30). In this context, considerable attention has also been given to the possibility that a superantigen, either retrovirally encoded or unrelated to HIV, may play an important role (35). Superantigens are microbial or viral antigens that can bind to T-cell subsets showing a specific variable region of the TCR- β chain (36). These superantigens therefore induce massive stimulation and expansion of T cells bearing the specific variable- β regions, followed by deletion or anergy (36). However, initial reports that patients with HIV infection have perturbations of T-cell subgroups bearing certain specific variable- β regions have not been confirmed. More importantly, the finding that apoptosis occurs spontaneously *in vitro* in the absence of an antigenic stimulus and that it occurs even in CD8⁺ T cells argues against the possibility that the mere activation of a prepared cell by a specific antigen or superantigen represents an important mechanism for the selective depletion of CD4⁺ Th cells (53).

T-cell precursors in the thymus or peripheral pools may be infected with HIV and therefore fail to proliferate and replenish the mature CD4⁺ Th lymphocyte population (44). The depletion of CD4⁺ T cells by HIV may also affect the overall homeostasis of T-cell populations (1). Finally, among the CD4⁺ T-cell subsets, HIV appears to infect and affect the function of memory cells more than naive cells (74). Recently, it has been suggested that the effects of HIV on T-cell responses during the asymptomatic stage reflect a switch from Th1 (helping cellular immunity) to Th2 (helping humoral immunity) cytokine profile, as also seen in many parasitic infections (18). However, several experimental approaches have failed to provide evidence of a Th1/Th2 switch, at least in most HIV-infected patients (68). At the most, a shift from Th1 to Th0 phenotype was observed in some CD4⁺ memory T cells from HIV-infected patients in initial or intermediate phases, whereas a preferential depletion of CD4⁺ T cells inducing the production of Th2-type cytokines was found in the advanced phase of HIV infection (49a, 49b). Moreover, CD4⁺ T-cell clones producing Th2 cytokines, when infected *in vitro* with HIV, appeared to be more efficient supporters of viral replication than Th1-like CD4⁺ T cells (49, 68). Taken together, these data suggest preferential HIV replication in Th2 cells

rather than induction by HIV of a Th1/Th2 switch (67).

Alteration of APC

Infected macrophages are important reservoirs outside the blood and act as carriers of HIV to different organs (the Trojan horse metaphor) (76). These nonproliferating, mature cells can sustain HIV production *in vitro* for a long time without being killed by the virus. Cytokine secretion by infected macrophages is also aberrant; this can lead to a cascade of secondary effects (see below). Macrophages act as APC particularly to memory T cells in the periphery. This interaction does not appear to be significantly impaired during the asymptomatic phase of HIV infection. However, the function of both macrophages and dendritic cells in bringing and presenting antigen to naive T cells in the lymph nodes is affected early in the course of HIV infection (41). Thus, patients may survive by their memory T-cell responses, but when these cells eventually become depleted, the lack of recruitment of new memory cells, which should have occurred through the interaction of APC with naive T cells, could contribute to immune deficiency.

Alterations of CD8⁺ T cells

CD8⁺ T cells play a dual opposite (protective and detrimental) role in HIV infection. In regard to the former, antigen-specific, cytotoxic T lymphocytes (CTL), normally important in combating viral infections, are readily detectable in HIV infection (56, 75). They have been detected in various tissues and can lyse target cells expressing HIV proteins, including *env*, *gag*, *pol*, *nef*, and *vif*. HIV-infected patients also possess CD8⁺ T cells that can suppress HIV replication *in vitro* by a nonlytic mechanism (56). A soluble CD8-derived factor appears to be involved, but the nature of this cytokine is still unclear (47). Closer examination of the CD8⁺ T-cell population in HIV-infected patients has revealed alterations in several subsets of CD8⁺ T cells. In particular, percentages of CD8⁺ T cells that express CD38, CD57, or HLA-DR increase early after HIV infection and usually continue to increase over time (47). More recently, a dramatic expansion of CD8⁺ T-cell subsets showing specific variable regions of the TCR- β chain has been found to occur early after infection in some patients (59). This oligoclonal CD8⁺ T-cell expansion appears to be strongly associated with faster progression toward the full-blown disease, suggesting a critical role for the CD8-mediated response in the development of the disease (59). Last, but not least, a switch of CD8⁺ T cells from the cytolytic Th1-like functional profile to Th2-like cells

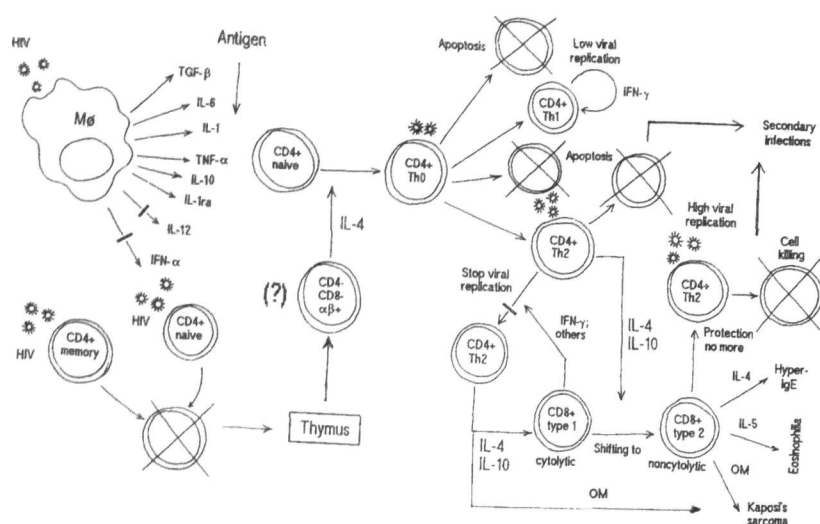


Fig. 2. Hypothetic model of progression to full-blown disease in patients showing KS, hyper-IgE syndrome and/or eosinophilia, in advanced phases of HIV infection. Defective production of IL-12 and IFN- α by HIV-infected macrophages (M ϕ) may favor development of IL-4 – producing cells even in response to Th1-inducing antigens (Th0 cells). Double-negative (CD4-CD8-) TCR $\alpha\beta$ + early thymic emigrants put into circulation since initial sharp decrease of mature CD4 + T cells may be another potential source of IL-4. CD8 + T cells eliminate HIV-infected CD4 + T cells by specific cytolytic activity or protect them from active HIV replication by nonlytic viral suppression. CD4 + Th1-like cells themselves are poor supporters of HIV replication, but they may die because of apoptosis induced by gp120 or gp120-anti-gp120 immune complexes. Th2 and Th0 cells which efficiently support HIV replication die rapidly because of either directly HIV-mediated cell killing or apoptosis; therefore, they are rarely detected in HIV-infected subjects. In some cases (probably because of genetic reasons), production of IL-4 and IL-10 may favor shift of CD8 + Th1-like cytolytic cells into CD8 + or double-negative, Th2-like, poorly cytolytic phenotype. Protective effect exerted by CD8 + T cells against HIV replication and other infectious agents is lost, and secondary infections by viruses and intracellular bacteria arise. Moreover, continuous production of IL-4, IL-5, and oncostatin M (OM) by HIV-uninfectable and therefore surviving CD8 + T cells can account for high IgE serum levels, eosinophilia, and (in association with other factors, see Fig. 4) development of KS, respectively.

showing B-cell helper function and reduced cytolytic activity has recently been detected by examining T-cell clones generated from the skin of HIV-infected patients with KS or the blood of some HIV-infected patients showing a Job-like, or hyper-IgE, syndrome (49b). This switch may explain, at least in part, the reduced defense against viral infections and intracellular parasites, and account for the elevated IgE serum levels, eosinophilia, and the allergic-like clinical manifestations seen in some HIV-infected patients (Fig. 2).

B-cell alterations

Although B cells are not directly infected by HIV, functional abnormalities of B cells, as well as of humoral immune responses, are common in HIV-infected patients. They include hypergammaglobulinemia; enhanced serum levels of IgG, IgA, and IgE (and also of IgM in children); the presence of cir-

culating immune complexes and autoantibodies; and *in vitro* spontaneous IgG production by circulating lymphocytes (7, 26). On the other hand, B-cell proliferation and immunoglobulin production induced *in vitro* by polyclonal activators, as well as primary responses *in vivo*, are impaired soon after HIV infection in most patients (43, 54). Mechanisms causing hyperactivation of the B-cell compartment in HIV-infected patients have not yet been clarified. Initially, B-cell hyperactivation was attributed to frequent association with infections by Epstein-Barr virus (EBV) and cytomegalovirus, which are well-known B-cell activators (26). Then, the direct B-cell-activating role of HIV components was adduced (26). However, experiments performed in various laboratories, including my own, have shown the T-cell dependence of B-cell hyperactivation (48, 78). CD4 + T cells infected *in vitro* with HIV acquire the ability to induce polyclonal B-cell proliferation and immunoglobulin production (45). Such a property was, at least in part, mediated by the constitutive expression of membrane tumor necrosis factor (TNF)- α , which mimics the CD40L-CD40 interaction (46), and in part by the continuous production of B-cell-activating cytokines, such as TNF- α , interleukin (IL)-6, and IL-10 (66).

NK cell alterations

Even NK cells, a very important cell type in the immune system because of their natural protective activity against viral infections and tumors, are profoundly altered (8). A reduction in both cytolytic activity and ability to produce interferon (IFN)- γ by NK cells from HIV-infected patients has been reported (8). Of note is the recent observation that, at least *in vitro*, this defect can be reversed by IL-12 (15), the production of which by HIV-infected macrophages appears to be defective (16).

Alterations in the cytokine network

Cytokines are important mediators of the immune system, where they act as both autocrine and paracrine physiologic inducers of the immune responses. In HIV infection, cytokines produced by cells of both "natural" and "adaptive" immune responses play a very important pathophysiologic role (Fig. 3). First of all, some cytokines upregulate HIV expression in infected cells. TNF- α upregulates HIV replication in chronically infected T-cell and macrophage lines, whereas IL-6 and granulocyte/macrophage-colony stimulating factor (GM-CSF) upregulate viral expression only on macrophage cell lines (61). The effect of TNF- α is mediated by nuclear factor-kB (NF-kB)-transactivating proteins, whereas IL-6 and GM-CSF mainly act at post-

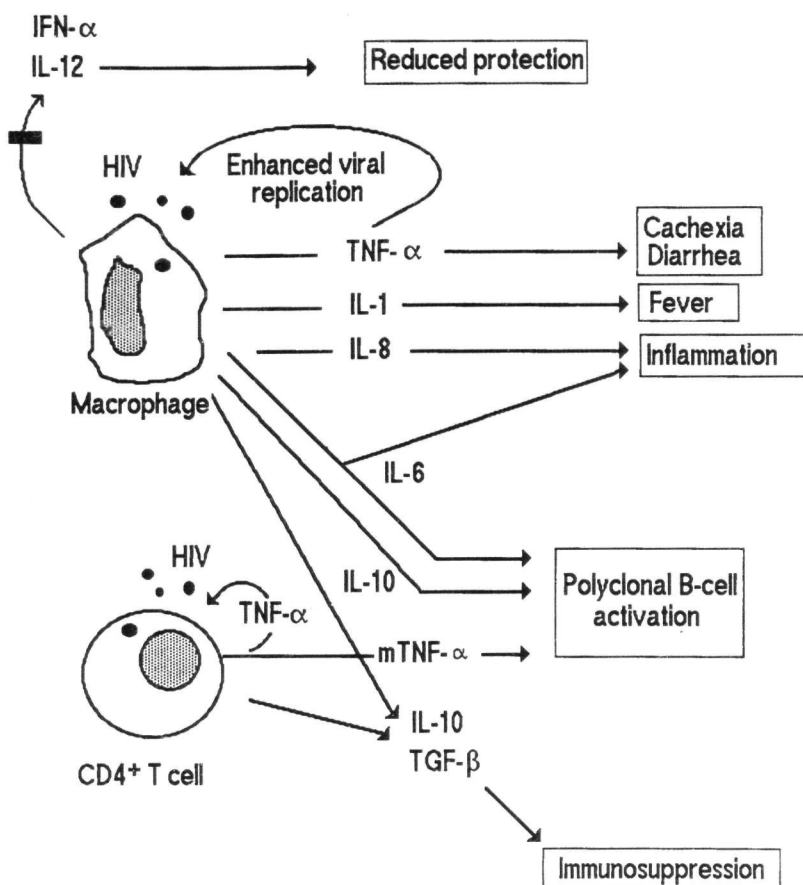


Fig. 3. Multiple effects of HIV-induced dysregulation of cytokine network. Reduced production of IL-12 and IFN- α by HIV-infected macrophages may inhibit development of CD4 $^{+}$ T cells into Th1-type cells and therefore account for reduced protection against infections by intracellular bacteria and viruses. Chronic production of TNF- α , IL-1 and IL-6 and chemokines (such as IL-8) by HIV-infected macrophages may account for fever, cachexia, diarrhea, and other inflammatory phenomena. Constitutive expression of membrane TNF- α by HIV-infected CD4 $^{+}$ T cells, together with production of IL-6 and IL-10, may account for polyclonal B-cell activation (hypergammaglobulinemia). Chronic and enhanced production of IL-10 and TGF- β may play important role in induction of immunosuppression.

transcriptional level (62). In contrast, other cytokines, such as IFN- α and transforming growth factor (TGF)- β , inhibit HIV replication (63). IFN- α mainly acts by inhibiting viral budding, whereas TGF- β exerts its inhibitory effect through both translational and posttranslational mechanisms (63).

Although the main function of cytokines is to transmit messages from cell to cell and they only rarely have systemic effects, their excessive and continued production in HIV infection can contribute to the profoundly altered homeostasis of HIV-infected patients. The clearest example is provided by TNF- α . Excessive TNF- α production not only contributes to enhanced HIV gene transcription (62), but also causes the wasting syndrome characteristic of the advanced phases of HIV infection ("slim disease") (69). Moreover, production of both TNF- α and IL-1 may cause unexplained fever and diarrhea in many patients, as well as other inflammatory phenomena, through the induction of IL-6 and chemokines. Lastly, the exaggerated production of TNF- α may account for the poor response of some patients to

zidovudine treatment, because of the inhibition exerted, at least *in vitro*, by TNF- α on the effect of this drug on HIV replication (66).

The dysregulated production of cytokines in HIV infection can also have a dramatically stimulating or suppressive influence on the function of the immune system. The possible role of constitutive membrane TNF- α expression and of enhanced IL-6, IL-10, and TNF- α production on polyclonal B-cell activation has already been discussed (25, 66). On the other hand, the exaggerated production of TGF- β may be partly responsible for the immunosuppression seen in the advanced phases of infection (2). Lastly, an imbalance in cytokine production by HIV-infected macrophages may favor the prevalence of Th2-like responses to some infectious agents. Macrophage production of IL-1, IL-6, IL-10, TNF- α , and GM-CSF is normal or increased, whereas production of IL-12 and IFN- α (both Th1-inducing agents) is defective in HIV-infected patients (16, 27). Because Th2-like CD4 $^{+}$ T cells are more efficient supporters of HIV replication than are Th1-like cells (49, 67), the combined defect of IL-12 and IFN- α may influence the enhanced expression of Th2-type cytokines, even in response to antigens usually evoking Th1 responses, and therefore favor HIV replication, HIV spread, and direct or indirect HIV-mediated T-cell killing.

Clinical aspects

Since the description of the first AIDS cases (10, 29, 50, 70), it has been clear that HIV infection can provoke a wide spectrum of clinical disorders, including the acute manifestations associated with the event of primary infection; systemic lymphadenopathy, which appears sooner or later in virtually all infected people during the long intermediate phase of clinical latency; severe and persistent constitutional symptoms; neurologic disorders; secondary neoplasms; and repeated or chronic opportunistic infections, as well as a severe wasting syndrome. The existence of so polymorphic a clinical spectrum has made it necessary to set up clinical classifications suitable for the definition of the different forms of the disease on the basis of homogeneous criteria. The Centers for Disease Control (CDC) classification (12, 13), which is currently used throughout the world and has recently been expanded (14), allows the division of HIV-infected patients into four main groups, and the fourth group into some subgroups (Table 2).

Acute disease

At 3–6 weeks after primary HIV infection, 50–70% of subjects develop an acute, self-limiting,

Table 2. CDC classification system of HIV infection

Group I	Acute infection
Group II	Asymptomatic infection
Group III	Persistent generalized lymphadenopathy (PGL)
Group IV	Other HIV-induced diseases
Subgroup A	Constitutional disease
Subgroup B	Neurologic disease
Subgroup C	Secondary infections
Subgroup D	Secondary tumors
Subgroup E	Other pathologic conditions

mononucleosis-like acute syndrome (38). It is associated with high levels of viremia, and it is followed within 1 week to 3 months by seroconversion (20, 22). The first anti-HIV antibodies to appear are anti-gp160 (envelope) antibodies, followed by anti-p24 (core) antibodies, and even later by anti-gp120 (envelope) antibodies. The HIV-specific immunity initiated during this stage is associated with a dramatic reduction of viremia (22, 38). However, while plasma viremia becomes difficult to detect even with very sensitive methods such as polymerase chain reaction (PCR), HIV expression persists in lymph nodes (24, 58), suggesting that viral replication is not completely curtailed with the emergence of an HIV-specific immune response. Although many patients with HIV infection do not have a clinically recognizable acute disease after primary infection, the biologic events described above probably occur even in the absence of symptoms.

Clinical latency

In all HIV-infected subjects, primary infection, either asymptomatic or associated with the acute disease, is followed by a long intermediate phase of clinical latency that lasts for years, even though its length may vary from subject to subject. The term "clinical latency" is misleading, however, because during this period virtually all patients show a gradual deterioration of the immune system, manifested particularly by the depletion of peripheral blood CD4+ T cells (57). This phase of clinical latency is mainly characterized by: 1) high levels of HIV-specific antibodies, probably resulting from persistent stimulation of the immune system by sporadic or chronic viral replication in lymphoid tissues; 2) low viral burden in the circulation, detectable only by highly sensitive PCR methods or sporadic measurement of low levels of p24 antigen; and 3) alterations in several immunologic variables (Table 3).

Persistent generalized lymphadenopathy (PGL)

Sooner or later during the course of HIV infection, virtually all subjects develop PGL, which is defined as an increase in lymph node size of more than 1 cm

Table 3. Main immunologic abnormalities detectable in HIV-infected patients

Lymphocytopenia
Reduction of relative and absolute numbers of circulating CD4+ T cells
Increase of relative and absolute numbers of circulating CD8+ T cells
Reduction or inversion of CD4/CD8 ratio
Reduction or absence of delayed-type cutaneous reactivity to recall antigens
Hypergammaglobulinemia
Increased serum levels of IgG and IgA (also IgM in children)
Increased serum levels of neopterin
Increased serum levels of β 2-microglobulin
Increased serum levels of soluble IL-2 receptors
Increased serum levels of soluble CD8 molecules

in diameter from at least two extralingual sites, persisting for at least 3 months in the absence of constitutional symptoms (11). The histologic picture of PGL is nonspecific, being characterized by hyperplastic lymphadenopathy with follicular hyperplasia in the initial and intermediate phases of infection, followed by follicular fragmentation and follicular atrophy in the final phase (5).

Constitutional disease

Before developing the full-blown disease, most HIV-infected subjects exhibit various constitutional signs or symptoms with or without PGL, but consistently associated with the typical immunologic alterations (Table 3). This syndrome, now called "constitutional disease", had been variably referred to as "AIDS-related complex", "Lesser AIDS", or "pre-AIDS" to indicate a phase of HIV infection clinically evolving toward the full-blown disease. The symptoms which characterize the constitutional disease are as follows: 1) fever lasting for 1 month at least; 2) diarrhea, lasting for 1 month at least (71); and 3) weight loss of at least 10% in the last 6 months. Obviously, these manifestations have to be present in the absence of other disorders that may account for their development (40, 77).

Neurologic disease

Neurologic disorders affecting HIV-infected subjects in the most advanced phases of infection are as follows: 1) AIDS-dementia complex (ADC); 2) vacuolar myelopathy; and 3) peripheral neuropathy. ADC, which is also called "subacute encephalitis" or "AIDS encephalopathy", occurs in about one-third of AIDS patients showing neurologic signs or symptoms (23, 73). These symptoms are initially obscure (loss of memory and concentration, slight depressive state, alterations of motility, and drowsiness), but they rapidly develop into real dementia, associated with both paralysis and lack of sensory functions. Vacuolar myelopathy has been documented in about 30% of HIV-infected people; it may

appear as ataxic spastic paraparesis with urinary and fecal incontinence (60). Peripheral neuropathies of the advanced phase are of the axonal, distal, mainly sensitive type. Clinically, they appear as painful paresthesia reminiscent of the more severe forms of alcoholic or diabetic neuropathy (52).

The pathogenesis of neurologic disorders in HIV infection is still unclear. HIV can infect macrophages, endothelial cells, and microglia cells in the central nervous system (CNS) and in the peripheral nervous system, but neurons are usually spared (52). At present, three main mechanisms have been proposed to explain the cerebral derangement in some HIV-infected patients: 1) secretion by HIV-infected macrophages and microglia cells of cytokines, especially $\text{TNF-}\alpha$, and other toxic factors for neurons; 2) competitive inhibition exerted by gp120 against neurotropic factors; and 3) suppressive activity of gp120 on neuronal function (52).

Neoplasms

Tumors significantly associated with HIV infection are KS, B-cell lymphomas, and the invasive carcinoma of the uterine cervix in females (14, 25). KS associated with HIV infection represents a new variant (epidemic KS) mainly affecting male homosexuals (42). Frequently, epidemic KS is characterized by multifocal, widespread, indolent, red-to-violet plaques or nodular lesions. Nearly all HIV-infected patients with KS develop a rapidly progressive disease, involving not only skin but also oral mucosa, lymph nodes, and visceral organs such as the gastrointestinal tract, lung, liver, and spleen (42). The pathogenesis of KS in HIV infection is still unknown, but the combined roles of HIV and another, still unknown agent, probably associated with orofecal sexual contact, have been suggested (43). Both viral factors, such as the product of the *tat* gene and chronic production of cytokines, and growth factors, such as IL-1, IL-6, TGF- β , oncostatin M, and basic and acidic fibroblast growth factor (FGF), are involved in its pathogenesis (Fig. 4) (43).

AIDS-related lymphomas usually are high-grade, pathologic type B-cell tumors, such as the small, uncleaved lymphoma and the immunoblastic lymphoma (42). The most typical form of HIV-associated B-cell lymphoma is the primary cerebral lymphoma, of which the most common presenting features are headache, cranial nerve palsies, seizure disorders, and hemiparesis, as well as rather subtle changes in personality, such as apathy. The pathogenesis of B-cell lymphomas in HIV infection is also complex and involves the combined role of the immune deficiency, chronic production of cytokines, and, sometimes, EBV activity (Fig. 5) (43).

Because of the combined activity of HIV and the

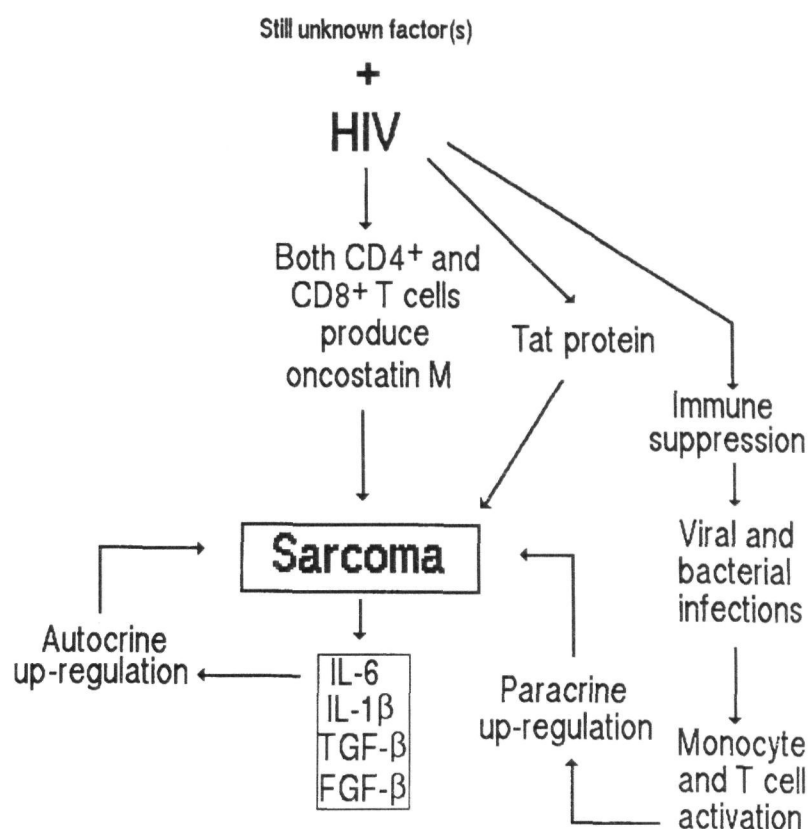


Fig. 4. Hypothetic model of development of AIDS-associated KS. HIV infection acts in genetically predisposed persons, probably in association with another sexually transmitted organism (mainly via orofecal contact). Expression of HIV *tat* gene may initiate process of cell (spindle cell of mesenchymal and perhaps smooth-muscle origin) transformation. This process may be associated with expression of certain receptors for, and therefore favored by activity of, cytokines such as IL-6 and OM. OM functions both directly and indirectly by induction of IL-6, which in turn functions as potent autocrine growth factor in AIDS-related KS. Other cytokines produced by both monocytes and T cells (e.g., $\text{TNF-}\alpha$, IL-1 β , TGF- β , and FGF) may also be associated with increased (paracrine) growth of KS.

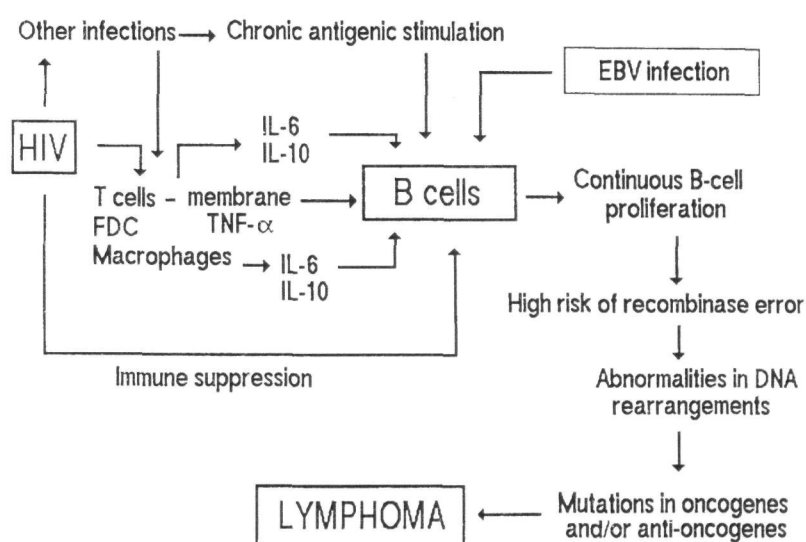


Fig. 5. Hypothetic model of development of AIDS-associated B-cell lymphomas. B-cell lymphomas arising in AIDS involve multiple factors, including underlying immunosuppression and chronic B-cell proliferation induced both by contact with HIV-infected activated Th cells and by B-cell-activating cytokines ($\text{TNF-}\alpha$, IL-6, and IL-10), HIV itself, EBV, or all three. This favors occurrence of recombinase errors, leading to DNA rearrangements and subsequent dysregulation of oncogenes, as well as inactivation of antioncogenes. While some of these factors may occur in most cases, no homogeneous patterns have been found, suggesting that distinct mechanisms of lymphogenesis may occur in different patients.

papilloma virus, the invasive cervical carcinoma has recently been recognized as a new indicator of AIDS in HIV-infected females (62). Other tumors, such as oral, tongue, and liver carcinoma; Hodgkin's lymphoma; and rhabdomyosarcoma (in HIV-infected children), have also been reported (25).

Secondary infections

Secondary infectious diseases, caused by either common microorganisms or opportunistic agents, certainly produce most of both the morbidity and the mortality in HIV-infected patients (Table 4).

PCP is the most important opportunistic infection, its prevalence ranging from 55% to 75% according to different surveys. The clinical picture of PCP is qualitatively the same as that of other infections in immunocompromised hosts (fever, nonproductive cough, tachypnea, dyspnea, hypoxemia, and respiratory acidosis), but it is quantitatively more obscure, sometimes showing a subacute or even chronic course. In the more typical cases, the chest radiograph reveals a diffuse reticulonodular infiltrate starting from the hilus, usually bilaterally (10). Diagnosis is established by directly detecting the presence of the parasite in the bronchoalveolar lavage (BAL) or in transbronchial biopsy (10). More recently, substantial improvement in the diagnosis of PCP has been achieved with the PCR method for the detection of the parasite in sputum, BAL, and blood.

Another very important opportunistic protozoan is *Toxoplasma gondii*. Toxoplasmosis exclusively localized in the CNS (neurotoxoplasmosis) is the most common opportunistic CNS infection in HIV-infected patients. Clinically, it presents as "pseudo-tumoral encephalitis", characterized by headache,

fever, and focal neurologic abnormalities such as hemiparesis and seizures (39). Computed tomography (CT) scan often reveals one or more focal abnormalities that are usually enhanced by contrast administration ("ring enhancement"). Definitive diagnosis of neurotoxoplasmosis requires histopathologic detection of the organisms in an involved cerebral area by stereotaxic biopsy (65). Because there is some risk associated with this procedure, *ex juvantibus* therapy can alternatively be used.

Cryptosporidium is another, very important genus of opportunistic protozoa in HIV-infected patients because of its species' ability to cause a highly weakening and intractable diarrhea. Diagnosis is mainly based on the microscopic detection of pathogens in stools (72). Other protozoans, such as *Isospora belli* and *Microsporidium*, as well as the nematode *Strongyloides stercoralis*, may cause severe gastrointestinal disorders in AIDS patients (39).

Fungal infections are a very common cause of localized or disseminated disease in patients with AIDS. The main opportunistic fungi belong to the following genera: *Candida*, *Cryptococcus*, *Histoplasma*, and *Coccidioides*. *Candida* mainly causes symptomatic mucosal alterations, but only rarely life-threatening diseases (10). Oropharyngeal infection by *Candida* affects virtually all AIDS patients and is often the first clinical manifestation; in contrast, lung, gastroenteric, ocular, and meningeal localization, as well as sepsis, are extremely rare (10). *Cryptococcus neoformans* is a fungus that commonly causes meningitis and disseminated disease in patients with AIDS. In this population, meningitis often presents subtly. Fever and headache are common, and nausea and vomitus may be seen in about half the patients, but stiff neck, photophobia, focal neurologic abnormalities, papilledema, and seizures are rare. Diagnosis of cryptococcosis requires documentation of the organism by culture or histopathologic analysis in cerebrospinal fluid or blood (79).

The most important bacterial infections in AIDS patients are certainly those of mycobacteria, particularly *Mycobacterium tuberculosis* and *M. avium intracellulare* (33). HIV infection has caused a significant increase in morbidity from tuberculosis, not only in underdeveloped countries but also in the USA, where there has been a 68% increase in the number of cases of tuberculosis between 1980 and 1989 (4). In AIDS patients, tuberculosis often presents both as extrapulmonary and as pulmonary localization, and it is usually characterized by drug resistance of mycobacteria. Infections by atypical mycobacteria usually occur after other opportunistic infections have already appeared. They cause disseminated diseases, characterized by fever, lymphadenopathy, diarrhea with abdominal pain, severe weight loss, or even cachexia. *M. avium intracellulare*, which alone

Table 4. Main secondary pathogens in AIDS

Protozoa	Viruses
<i>Pneumocystis carinii</i>	Herpes simplex
<i>Toxoplasma gondii</i>	Herpes varicella-zoster
<i>Cryptosporidium</i> spp.	Cytomegalovirus
<i>Isospora belli</i>	Epstein-Barr virus (EBV)
<i>Microsporidium</i>	Progressive multifocal encephalopathy virus
Fungi	Metazoa
<i>Candida</i> spp.	<i>Strongyloides stercoralis</i>
<i>Cryptococcus neoformans</i>	
<i>Histoplasma capsulatum</i>	
<i>Coccidioides immitis</i>	
Bacteria	
Mycobacteria	
<i>Salmonella</i> spp.	
<i>Legionella pneumophila</i>	
<i>Nocardia asteroides</i>	
<i>Streptococcus pneumoniae</i>	
<i>Staphylococcus epidermidis</i>	
<i>Haemophilus influenzae</i>	

causes more than 90% of all atypical mycobacteriosis, can be isolated from blood, stools, urine, bone marrow, lymph nodes, intestinal wall, BAL, or biopsy specimens of various organs (9).

Unlike atypical mycobacteriosis, infections by *Salmonella* may appear very early in HIV-infected patients, usually before any other clinical manifestation. A typical feature of salmonellosis in HIV infection is the consistent presence of both bacteremia and positive coproculture, making the diagnosis easy (39).

Among opportunistic viral infections, that of herpes simplex (HS) most frequently causes mucocutaneous disease in HIV-infected patients (83). The most common clinical manifestation in male homosexuals is indeed HS-induced perirectal ulceration (39). The herpes varicella-zoster virus usually causes a dermatomeric form which is not specific for HIV infection, but represents an early marker of immunosuppression in these patients. More rare is the disseminated form, either as consequence of the dermatomeric form or as its first manifestation (51). Most AIDS patients also suffer from cytomegalovirus-induced retinochoroiditis. Cytomegalovirus infection usually presents as asymptomatic retinal alterations ("cotton wool" type) which do not require therapy, but sometimes it provokes retinal hemorrhages and visual acuity disturbances. Diagnosis is based on funduscopic examination (34). Another early and frequent viral complication in HIV-infected patients is hairy leukoplakia, which is caused by EBV. This manifestation is usually well tolerated by the patient, but is an important predictor of development toward the full-blown disease (66).

Other abnormalities

In addition to the typical alteration of immunologic variables (see above), some HIV-infected patients may also have hematologic abnormalities, such as anemia, leukopenia, and thrombocytopenia (37). The pathogenesis of thrombocytopenia is complex, reflecting in part the activity of platelet-bound immune complexes and in part HIV-induced bone marrow damage, as suggested by the beneficial effect exerted in some patients by zidovudine therapy (78). In most patients, however, hematologic manifestations remain asymptomatic and do not require any treatment.

Concluding remarks

AIDS was probably the most rapidly recognized pathologic condition in the history of biomedical research. There is no longer any doubt that AIDS is the end-stage disease of HIV infection. Within a few years of the description of the first AIDS cases, both

the cause and the natural history of, as well as the complex clinical spectrum resulting from, HIV infection have been clarified. Many of the pathogenic mechanisms associated with HIV infection that lead to clinical disease have been established, such as the functional abnormalities and the quantitative depletion of CD4+ T cells that cause the profound immunosuppression characteristic of advanced HIV infection. We also know that other cells, especially tissue macrophages and FDC, become infected, and that there is a considerable viral load in the lymph nodes throughout the course of infection. However, some questions that seem to be very important for the development of therapeutic strategies remain unanswered. It is not yet clear whether HIV infection is the only cause of CD4+ T-cell depletion or whether AIDS is also an autoimmune disease triggering apoptosis. The role of macrophages and other APC in the development of the immune derangement is still obscure. The mechanisms determining the imbalance in cytokine production by infected macrophages, as well as those determining the alternate phases of immune activation and immunosuppression, are unclear. The importance of viral mutations in overcoming of the immune system by HIV also remains to be elucidated. On the other hand, the evidence is accumulating to suggest that early in infection the cellular and humoral immune responses to HIV appear to be effective in limiting viral replication in peripheral blood cells. More importantly, in a minority of HIV-infected patients (the so-called long-term survivors), HIV-specific immune responses seem to be highly effective in preventing HIV spread and HIV-mediated immune derangement. Thus, it will be very important to establish to what extent this is due to differences in virulence of HIV strains, and to what extent it reflects genetic variation in infected hosts. Finally, the question of whether or not severe immunosuppression resulting from the deficiency in T cells and the wasting/CNS disease are distinct attributes of AIDS also needs to be clarified. We should, however, be aware that AIDS pathogenesis is very complex and that the many ideas on how HIV causes this syndrome are probably not mutually exclusive.

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