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Molecular virology and immunology of HIV infection

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Great progress has been made with respect to our understanding of the immunopathogenesis of AIDS and the infectious agent, HIV, that causes the disease. HIV, a human retrovirus with tropism for CD4⁺ T cells and monocytes, induces a decrease of T-cell counts, T-cell dysfunction, and, ultimately, immunodeficiency. HIV also causes B-cell dysfunction characterized by polyclonal activation, hypergammaglobulinemia, and lack of specific antibody responses. Chemokine receptors—mainly CCR5 and CXCR4—have been found to be necessary for viral entry into the host cell, a step that can be inhibited by chemokine-related molecules that are ligands for those receptors. After HIV infection, a strong cellular immunity develops and partially controls viral replication. It can take several years for HIV infection to become clinically evident. Studies in long-term nonprogressors have shown the determinant roles of both helper and cytotoxic T cells in the control of HIV disease. Advances in HIV immunology research are currently being applied in the development of prophylactic and therapeutic vaccines. (*J Allergy Clin Immunol* 2002;110:189-98.)

Key words: HIV, AIDS, chemokine, cytokine, vaccine, immunology, CD4, lymphocyte, monocyte

The increased frequency of infections occurring in patients with primary and secondary immunodeficiencies provides direct evidence of the essential role of the immune system in the control of infectious agents. HIV is a particular adversary, because its primary target is precisely the immune system itself, making the host unable to control the virus and at the same time more susceptible to infections by other pathogens. Great progress toward an understanding of the pathogenesis and control of HIV infection has been made since the first HIV-

Abbreviations used

cDNA: Complementary DNA
HLA: Human leukocyte antigen
MHC: Major histocompatibility complex
MIP: Macrophage inflammatory protein
NFκB: Nuclear factor κ of B cells
SIV: Simian immunodeficiency virus

infected patient was reported more than 20 years ago. Current antiretroviral drugs have decreased HIV-related morbidity and mortality by reducing the viral load and increasing CD4⁺ T-cell numbers.^{1,2} The newest mathematical models that incorporate the concept of HIV reservoirs predict that antiretroviral therapy would take at least 60 years of complete viremia suppression to eradicate the virus from the host.³ This estimate points out the importance of the immune system in control of HIV disease and its progression to the most severe clinical stage, AIDS.

This review summarizes current concepts of molecular virology and immunology related to HIV infection that are useful to an understanding of its pathogenesis and clinical manifestations; also reviewed are current efforts to control the HIV epidemic.

MOLECULAR VIROLOGY OF HIV

HIV is a lentivirus, from the family of retroviruses, which characteristically have an RNA genome contained within a capsid and a lipid envelope (Fig 1).

Viral structure

The viral envelope, a bi-layered membrane derived from the host cell, contains 2 major viral glycoproteins, gp41 and gp120. These originate from enzymatic cleavage of the larger viral pre-protein gp160; they mediate viral entry and syncytium formation. Gp120 has a variable protein domain containing the V3 loop, which elicits a strong immune response.⁴ The HIV core is composed of 3 structural proteins, p24, p16, and p9. The p24 protein forms the capsid that encloses 2 genomic RNA strands and the viral enzymes. The matrix protein, gp16, is anchored to the internal face of the envelope. p9 is a nucleocapsid protein not covalently attached to the viral RNA.⁵

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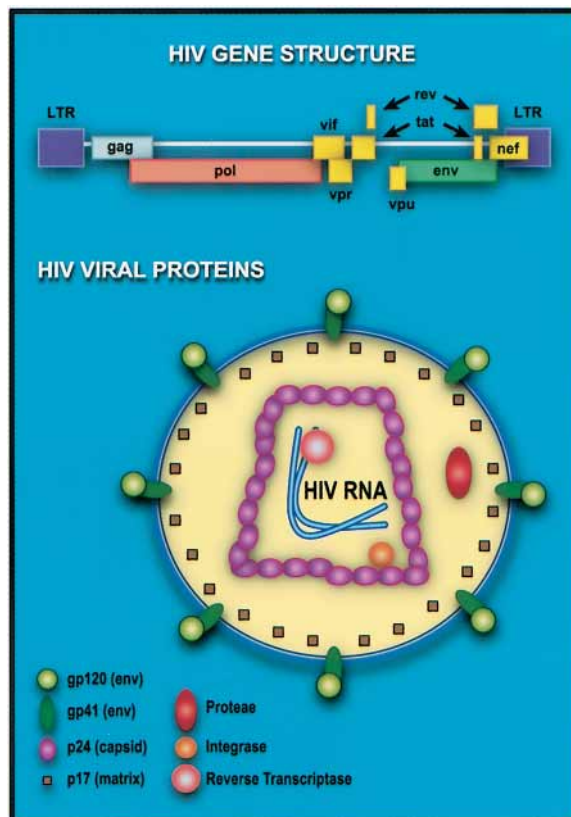


FIG 1. HIV viral proteins and gene structure.

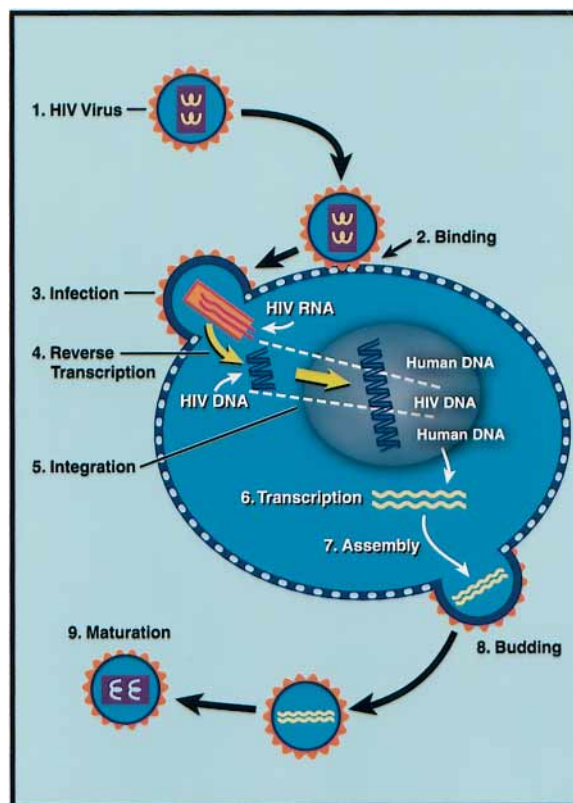


FIG 2. HIV replication.

TABLE I. HIV gene products

Structural proteins	Regulatory proteins
Envelope: gp41, gp120	Transcription regulators: Tat, Rev
Core: p24 (capsid) p16 (matrix) p9 (nucleocapsid)	Other: Vif Vpu Vpr Nef

Different viral subtypes are associated with different degrees of virulence and transmissibility. On the basis of nucleotide sequence identity of the env and gag genes sequences, HIV strains have been classified into 3 groups: M (majority), O (outliers), and N (non-M/non-O). Group M has 10 different subtypes, designated clades A through J. Clade B is the most common in the United States and Western Europe; clades A, C, D, and E are most common in the developing world. Epidemiologic studies have shown that clade E is associated with a higher rate of heterosexual transmission than clade B. Differences in vertical transmission and progression rates have also been reported among these strains.⁶

HIV has 6 regulatory proteins: Tat, Rev, Nef, Vif, Vpu, and Vpr (Table I). Tat and Rev regulate viral gene transcription and are essential for HIV replication. Vif increases the efficiency of HIV infection in vitro. Vpu intervenes in the assembly process and Vpr in the nuclear transport of the viral genome. Nef might have multiple functions, including acceleration of clinical disease, enhancement of virion infectivity, downregulation of surface CD4 and MHC class I molecules, modulation signal transduction, and the favoring of HIV entry into target cells by the CD4 and chemokine-dependent route.⁷

Mechanism of replication

HIV enters lymphocytes and monocytes (Fig 2) through cognate recognition of the viral glycoprotein gp120 with the cell surface CD4 molecule and a chemokine receptor (either CXCR4 or CCR5; Fig 3).⁸⁻¹⁰ The interaction of these proteins induces the binding of the viral gp41 to heparan sulfate on the host plasma membrane; this triggers the fusion of the viral envelope and the release of the capsid into the cytoplasm.^{11,12} On the basis of cell tropism, HIV strains can be broadly divided into 2 categories, macrophage-tropic (M-tropic) and T-cell tropic (T-tropic). M-tropic strains use CCR5 as a coreceptor and are referred as *R5 viruses*. They primarily infect macrophages and primary T cells and infect poorly CD4⁺ T-cell lines. In addition, these viruses tend to be transmit-

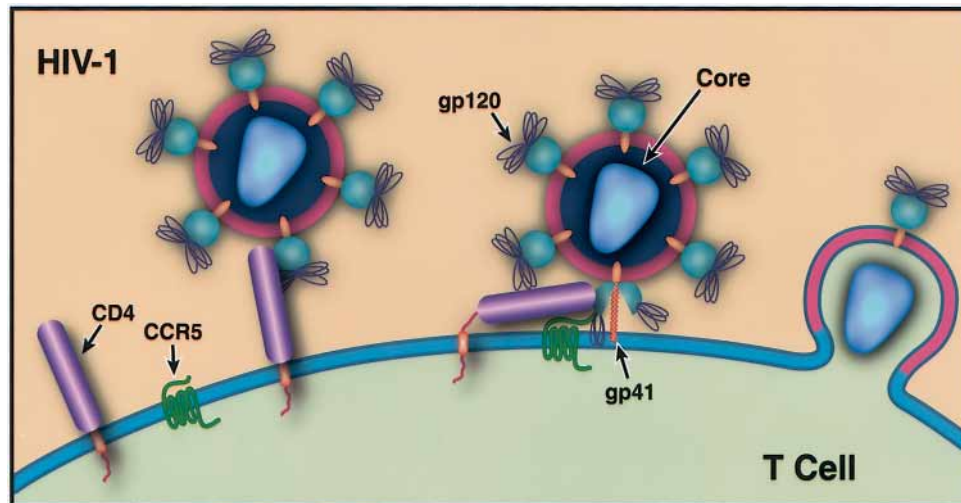


FIG 3. HIV viral entry. Modified from an image at the public Web site of the National Institute of Allergy and Infectious Diseases (<http://www.niaid.nih.gov/daids/dtpdb/attach.htm>).

ted sexually more easily.¹³ T-tropic strains use the CXCR4 coreceptor, which is most expressed in CD4⁺ T cells. Also referred as *X4 viruses*, they induce the formation of syncytia in the infected cells.^{14,15} Early in the course of HIV infection, the R5 strain viruses predominate, but eventually both X4 and R5 strains are recovered. Mutations in the CCR5 gene protect cells from HIV infection. These mutations have not shown to be deleterious, probably because other chemokine receptors replace CCR5 functions.¹⁵ The level of expression of chemokine receptors also determines the ability of HIV strains to infect host cells.^{16,17} Recently, a primary HIV isolate has been reported to enter T cells using the CD8 molecule, not requiring CD4 or chemokine receptor expression.¹⁸ Proposed strategies to inhibit the entry step include the use of CD4-binding molecules, β -chemokines, and the peptide T series that resemble and block gp41 function.¹⁹

Immediately after entry, the viral capsid releases the virus RNA genome and viral proteins into the cytoplasm. The viral RNA is reverse-transcribed into complementary DNA (cDNA) by the virus reverse transcriptase through use of a cellular lysine tRNA molecule as a primer²⁰; subsequently, the RNAase activity of the reverse transcriptase degrades the viral RNA template. The reverse transcriptase incorporates an incorrect nucleotide every 1500 to 4000 bases, which explains the rapid occurrence of mutations. Some of the resulting mutations provide a survival advantage, leading to drug-resistant strains.²¹ Several nucleoside and non-nucleoside inhibitors of the reverse transcriptase have been developed.²² The newly synthesized HIV-1 cDNA is transported to the nucleus. Two HIV proteins, Vpr and Vif, might participate in this nuclear transport. Vpr is thought to enhance the HIV-1 preintegration complex transport to the nucleus.²³ Vif associates with cytoskele-

tal elements and increases the infectious potential.²⁴ Once in the nuclear membrane, peptide sequences from Vpr and the matrix protein provide a nuclear localization signal to enter the nucleus. The viral cDNA integrates randomly into the host cell genome in a reaction catalyzed by the viral enzyme integrase. Inhibitors of this enzyme are under development.²⁵

After integration, cellular transcription factors are able to activate viral gene transcription, producing low levels of short, multiply spliced mRNA transcripts. They encode the regulatory proteins Tat, Rev, and Nef. Tat transactivates transcription by binding the 5' end of the viral DNA sequence, increasing the viral transcription rate 1000-fold.²⁶ Rev binds an RNA structure in the env gene region and mediates the nuclear export of incompletely spliced transcripts. Rev favors the export of partially spliced mRNA transcripts encoding structural proteins and full-length mRNA transcripts that constitute the viral RNA genome.²⁷ Inhibition of Tat or Rev significantly impairs HIV replication. Several gene therapy strategies to inhibit these 2 functions have been tested in vitro with relative success.^{27,28}

The components of the HIV viral core are initially translated into pr55, a pre-protein resulting from a long, singly spliced gag mRNA and then cleaved during maturation. Gag-Pol is another pre-protein that is cleaved to produce the viral enzymes protease, integrase, and reverse transcriptase. HIV protease mediates the specific cleavage of these pre-proteins, and its inhibition results in marked suppression of viral replication.²² Pr55 and Gag-Pol are the result of 2 reading frames that also control the relative amount of these proteins to produce more structural components than viral enzymes. The first reading frame encodes pr55 and is more efficient than the second, which is responsible for Gag-Pol synthesis.²⁹ An

TABLE II. Major immunologic abnormalities induced by HIV infection**Cellular**

Lymphocytes: CD4 lymphopenia; decreased naive phenotype and lymphoproliferation

Decreased delayed hypersensitivity skin test response to recall antigens

Monocytes: decreased phagocytosis, chemotaxis, intracellular killing, and cytokine expression

Neutrophils: neutropenia; decreased phagocytosis and intracellular killing

NK cells: Decreased natural killer cell-mediated cytotoxicity

Humoral

Decreased B-cell number; polyclonal activation of B cells

Increased production of nonspecific immunoglobulins G, A, and M

Loss of specific antibody responses

intermediate-length mRNA produces gp160, which migrates to the cell membrane and is cleaved during the virion formation to originate the regulatory proteins Vpr, Vpu, and Vif and the envelope proteins gp41 and gp120. These proteins and host membrane proteins are incorporated on the plasma membrane to form the viral envelope around the capsid, which already contains the viral RNA genome. The assembly process is energy-dependent and likely involves unidentified cellular factors.³⁰ Gp160 can be cytopathic by binding to CD4 and altering the protein traffic in the cytoplasm. Vpu induces degradation of CD4 and might play a role in the gp120 processing for a functional envelope as well as in the downregulation of CD4 surface expression.³¹ Vpu interacts with ubiquitin molecules and mediates degradation of phosphorylated I κ B kinase and reduction of NF κ B activity.^{31,32}

MOLECULAR IMMUNOLOGY

HIV infection induces a profound immune dysfunction, with abnormalities in every arm of the immune system (Table II). The study of long-term nonprogressors (HIV-infected patients who are asymptomatic and have normal CD4⁺ T-cell counts in the absence of treatment) has revealed that several immune mechanisms are significant in controlling HIV infection. Such patients might have low but detectable viremia, which seems to be important in maintaining the host-specific immune response. These mechanisms include the following: (1) increased production of T_H1-type cytokines, such as IL-2 and IFN- γ , (2) HIV-specific CD4⁺ T-cell proliferative responses and cytotoxic CD8⁺ T-cell activity, and (3) increased synthesis of CD8⁺ T-cell suppressive factors and β -chemokines. HIV has several inherent strategies by which to escape this vigorous immune response and continue replicating. The most studied of these strategies are antigenic variation,^{33,34} downregulation of the surface expression of MHC molecules, and reduction of specific CD8⁺ T cells.³⁵

The humoral immune response

HIV does not replicate in B cells but produces severe B-cell dysfunction, mediated by viral proteins toxicity and cytokine dysregulation.³⁶ HIV-infected patients present with B-cell hyperplasia, circulating immune complexes, elevated autoantibodies, and polyclonal hypergammaglobulinemia, with approximately 20% specific anti-HIV antibodies.^{37,38} Ultimately, HIV infection leads to B-cell depletion.³⁹ There is an impairment in the production of specific antibodies to new and recall antigens and both T-dependent and T-independent antigens.^{40,41} Recently, a subpopulation of B cells with low CD21 expression has been described in high-viremia patients. These cells are enhanced immunoglobulin secretors and poor antibody responders and might be partly responsible for the humoral defects in HIV infection.⁴² HIV gp120 protein modulates B-cell function, apparently by binding the VH3 domain of the membrane immunoglobulin, similar to superantigens.^{36,43} HIV might use specific antibodies to gain entry into mononuclear cells, taking advantage of the enhanced phagocytosis of opsonized particles.

HIV activates complement through alternative and classic pathways.^{44,45} Although complement C3 is deposited on the viral surface, there is poor function of the complement C5-C9 membrane attack complex. HIV might infect cells using complement receptors. Soluble CD16 has been shown to inhibit C3 receptor-mediated HIV-1 infection of monocytes.^{46,47}

Experiments in primates have shown that passive HIV-specific antibody transfer might be useful as protection against HIV infection, and IgG3 appears to have more neutralizing potency than IgG1, according to results of in vitro assays to block viral fusion.⁴⁸ However, passive antibodies might induce a selective pressure on viral replication, resulting in virus escape mutants.⁴⁹ In acute infection, partial viral clearance occurs before the specific antibody response is generated. There is a general lack of correlation between the magnitude of the humoral response and the decrease of viral load. These facts argue against a significant role of neutralizing antibodies in controlling HIV infection.⁵⁰⁻⁵²

The cellular immune response

HIV induces a strong and efficient cellular immune response; however, the infection is only partially controlled. This apparent contradiction can be explained by the several viral mechanisms of immune evasion: HIV provirus latency, sequestration reservoirs, switch of viral strain from R5 to X4, downregulation of MHC molecules, upregulation of Fas ligand, and viral protein epitope mutations.⁵³

The decrease of total lymphocyte number and CD4⁺ T-cell count and percentage are markers for HIV disease progression in children and adults. CD4⁺ T cells are also known as *helper T cells*, because they produce cytokines and interact with other immune cells to orchestrate the immune response.⁵⁴⁻⁵⁶ Before the decline of T-cell num-

bers, T-cell function abnormalities can be demonstrated by a reduced lymphoproliferative response to antigens and to mitogens.^{40,57} Long-term nonprogressors and patients responding to anti-HIV treatment demonstrate good lymphoproliferative responses, mainly to Gag protein. This response often correlates with decreased viral load and a strong T_H1-type cytokine production.⁵⁸⁻⁶⁰ Although HIV preferentially infects memory CD4⁺ T cells (CD45RO⁺), the T-cell depletion is more pronounced in naive cells (CD45RA⁺CD62L⁺). Memory T-cell counts are presumably preserved as a result of chronic stimulation.^{61,62} The T-cell repertoire is disturbed and restricted.⁶³ The rates of most common opportunistic infections are markedly reduced after initiation of antiretroviral therapy, but a similar reduction has not been observed in the incidence of other infections and lymphomas, suggesting that the T-cell repertoire is not completely restored and that long treatment periods are needed.⁶⁴

HIV infection depletes CD4⁺ T cells by inducing apoptosis, impaired production, or redistribution into lymphoid organs.⁶⁵ In HIV-infected patients, there is evidence of accelerated destruction of CD4⁺ T cells with death of both infected and noninfected T cells.^{66,67} This cell death involves several mechanisms: Env-mediated apoptosis, Vpr-induced cell-cycle G2 arrest, disruption of cell-membrane syncytia formation, cytolysis by natural killer or cytotoxic cells, and autoimmune reactions. HIV, especially the X4 strains, infects the thymus, with destruction of the stromal support and decreased cytokine production.^{68,69} HIV is present in the bone marrow and can cause lymphopenia, neutropenia, anemia, and thrombocytopenia. The HIV-induced bone marrow changes usually reverse with antiretroviral therapy.⁶⁵ It has been reported that dendritic cells expressing the dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin binds HIV in the peripheral tissues without being infected and transports the virus to lymph nodes and organs where CD4⁺ T cells are present.⁷⁰

Specific cytotoxic CD8⁺ T cells kill HIV-infected cells with CD4⁺ T-cell help that is needed to prime CD8⁺ T-cell responses and maintain both immunologic memory and the cytolytic response. In animal models (mainly in macaques), it has been shown that CD8⁺ T-cell depletion is associated with increased viremia.^{71,72} During acute infection, the CD8⁺ T-cell count increases up to 20-fold, with a vigorous specific HIV response.^{50,73} Most of these cells are activated and associated with disease progression in adults and children.^{74,75} CD8⁺ T cells contribute to antiviral activity by their HIV-specific cytotoxicity and by secreting soluble factors that inhibit HIV replication.⁷⁶ Specific anti-HIV cytotoxic CD8⁺ T cells are found a few weeks after infection, even before specific antibodies are detectable.⁵⁰ However, their number declines with advanced disease.⁷⁷⁻⁸⁰ These cells are present regardless of disease stage—up to 1% to 2% in chronic infection and up to 8% in acute infection, even in the absence of peripheral CD4⁺ T cells.^{79,81,82} The association of CD4⁺ T-cell help and a robust CD8⁺ T-cell response in HIV infection⁸³ is supported by experimental data showing an inverse cor-

relation between HIV-specific CD8⁺ T cells and viral load. In addition, CD8⁺ T cells from HIV-infected patients exhibited impaired cytokine responses and cytolytic activity, whereas CMV-specific CD8⁺ T cells from the same patients were normal.⁸⁴ This impairment correlated with lack of T-cell maturation and length of AIDS-free survival period.^{82,84,85}

Human leukocyte antigen in HIV infection

The importance of human leukocyte antigen (HLA) molecules in antigen presentation has prompted studies to determine the association of specific HLA alleles and HIV disease progression. It has been shown that a single amino acid change in HLA molecules modifies the rate of progression to AIDS. HLA B35 is the most common allele associated with development of AIDS. A2, B27, B51, and B57 are associated with better clinical outcome. These phenotypes do not change the susceptibility to HIV infection.⁸⁶⁻⁹⁰

Cytokines

Clerici et al⁹¹ showed that progression of disease was associated with a switch of cytokine response from T_H1 to T_H2. T_H1-type cytokines help to induce the strong cellular response that is responsible for the initial control of viremia. HIV-1 infection modifies the secretion of IL-1, IL-2, IL-6, IL-7, IL-10, IL-12, IFN- γ , TNF- α , and other cytokines, depending on disease progression.⁹²⁻⁹⁶ The influence of cytokines in HIV pathogenesis is diverse and not completely understood. They might also be involved in the decline of natural killer cell function, which has been shown to be restored when cytokines are added in vitro.⁹⁷ Leukemia inhibitor factor inhibits HIV-1 replication and is increased more often in the placentas of mothers that do not transmit HIV-1.⁹⁸ IL-7 favors the persistence of HIV through inhibition of apoptosis in thymocytes and lymphocytes, converting these cells in viral reservoirs.⁹⁹

Chemokines

The chemokine receptor CCR5 is expressed 8-fold higher in T_H1 cells than in T_H2 cells, and CXCR4 is expressed 4-fold higher in T_H2 cells than in T_H1 cells. In addition, T_H2 cells preferentially support HIV X4 viruses and T_H1 cells better support HIV R5 viruses; however, R5 strains eventually replicate better in T_H2 cells. These results are in concordance with the evolution of the HIV tropism phenotype in infected patients, from R5 initially to X4 predominantly during the late stages of the disease.^{100,101}

CD8⁺ T cells secrete the β -chemokines RANTES, MIP-1 β , and MIP-1 α , which are CCR5 natural ligands and suppress HIV-1 replication. Similarly, the alpha chemokine SDF-1- α is the only natural ligand for CXCR4 and blocks its interaction with gp120, inhibiting HIV-1 entry.^{102,103} A study of 347 HIV-infected individuals found a correlation between mitogen lymphocyte proliferation, MIP- β synthesis, and decreased disease progression.¹⁰⁴ Chemokines might also play a role in

TABLE III. Selected anti-HIV vaccine strategies

Authors	Year	Strategy, antigen	Comments
Davis et al	2000	VEE vector, SIV Env	Targets dendritic cells, elicits strong humoral and cellular response
Crotty et al	1999	Poliovirus vector, SIV Env	Oral route, induces systemic mucosal immune response
Seth et al	2000	Vaccinia vector, SIV Gag-Pol	Protective Gag-specific CTLs (macaque model)
TAVEGP	2001	Canarypox vector, HIV Env, Gag, Pol	30% of vaccines developed CTLs, weak neutralizing antibodies
Shiver et al	2002	Adenoviral vector and protein booster, HIV Gag	Most efficient strategy to develop anti-HIV cellular immunity
Lambert et al	1998	Recombinant peptide, HIV gp120, gp160	30% to 60% of vaccines with lymphoproliferative responses
Borkowsky et al	2000	Recombinant peptide, HIV gp120	56% of vaccines developed lymphoproliferative responses
Boyer et al	2000	DNA vaccine, HIV env/rev	Induction of strong cellular response
Liszewicz et al	2000	DNA-transduced dendritic cells, HIV env/gag	Strong cytotoxic response in a macaque model

VEE, Venezuelan equine encephalitis.

vertical transmission; Wasik et al¹⁰⁵ found that uninfected HIV-exposed children did not have increased HIV-specific cytotoxic cells but did secrete more chemokines. The therapeutic use of chemokines to inhibit HIV entry is currently being tested, though it seems that large concentrations are needed to produce a significant inhibitory effect.¹⁰²

VACCINE DEVELOPMENT

An effective vaccine that prevents HIV infection is a world research priority, given the extent of HIV epidemics and the relatively high cost of available antiretroviral drugs. In addition to the prevention of infection, vaccine goals include the prevention or reduction of HIV disease progression and the induction of sterilizing immunity for virus eradication.¹⁰⁶ Among the more than 20 candidate vaccines that have been tried in human beings are Env subunits, gp120, gp160, multimeric gp120, and V3 peptides (Table III). Viral vectors have been used to enhance immunogenicity (eg, vaccinia virus with gp160 and canarypox virus with Env, Gag, Pol, and Nef). Alphaviruses, poliovirus, adenovirus, adeno-associated virus, herpes virus, rabies, and vesicular stomatitis virus are also being investigated as potential vaccine vectors.¹⁰⁶ Venezuelan equine encephalitis virus vectors have been used to target dendritic cells, which are efficient antigen-presenting cells. Venezuelan equine encephalitis–simian immunodeficiency virus (SIV) hybrid has provided partial protection against challenge and has elicited both humoral and cellular responses in macaques.¹⁰⁷ Adenoviral and poliovirus vectors have been used to stimulate the mucosal immune system of macaques through nasal and oral immunization, respectively, with moderate protection against vaginal challenge in macaques and induction of systemic mucosal response.^{108,109} Initial vaccine efforts focused on Env-

derived peptides, which have been shown to induce an antibody response with poor viral neutralizing efficacy.¹¹⁰ Other studies have provided evidence for the need to induce a specific CD8⁺ T-cell response. Sex workers resistant to HIV infection do not have HIV-specific antibodies but make a strong specific CD8⁺ T-cell response. Induction of virus-specific CD8⁺ T cells protects macaques from SIV infection.^{111,112} A vaccine protocol involving priming with SIV-env gene in vaccinia and a boost with Env protein protected completely against SIV infection; however, the protection was only for a homologous viral challenge—a fact that underscores the importance of using epitopes that are shared by most strains.¹¹³ A different protocol with Gag-pol genes in a modified vaccinia virus showed that the induction of cytotoxic T-cell Gag epitopes correlated with SIV viremia reduction, similar to the association of CD8⁺ T cells and disease progression found in human beings.^{50,114} To date, few HIV vaccines have been tested in phase I trials and demonstrated to be safe, though only modest levels of HIV-specific CD4⁺ and CD8⁺ T-cell responses have been elicited. A canarypox vaccine carrying Env, Gag, and Pol epitopes has shown to induce a response that lasts up to 9 months in uninfected subjects. One third of vaccines develop anti-HIV cytotoxic T cells and have weak neutralizing antibodies, though these can be boosted with a dose of recombinant viral proteins.¹¹⁵⁻¹¹⁸ Recombinant HIV envelope proteins are also being studied, but their protection is limited to the strain used, inducing antibodies with poor neutralizing capacity.^{119,120}

DNA vaccines offer the advantages of low cost, simplicity, and fewer storage requirements.¹²¹ A few vaccine candidates are already in phase I trials. Through use of DNA plasmid carrying env and rev genes, they have been shown to induce strong T-cell responses as well as increased chemokine secretion in non-HIV-infected volunteers.¹²² To improve the immunogenicity of DNA vac-

cines, several strategies are being tested, including the coadministration of cytokine-encoding plasmids or immunostimulatory DNA sequences. In mice, DNA strategies elicit good mucosal specific antibodies and cytotoxic activities.¹²³ Lisiewicz et al¹²⁴ transduced dendritic cells with DNA plasmids encoding HIV Env and Gag proteins and infused them back into nonhuman primates. They produced a strong cytotoxic response and high cytokine production in response to viral challenge.

CONCLUSIONS

Progress in molecular virology and immunology has revealed the importance of the cellular immune response in the control of HIV infection. The presence of anti-HIV cytotoxic CD8⁺ T cells correlates with decrease of viremia, though HIV-specific CD4⁺ T cells are needed to maintain an efficient response. Current efforts to develop an anti-HIV vaccine are aimed at eliciting similar cellular responses in addition to antibody responses. Several critical issues remain unresolved, including the influence of genetic factors in the resistance to infection, the role of chemokines, and the persistence of viral reservoirs.

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