

Host Determinants in HIV Infection and Disease

Part 2: Genetic Factors and Implications for Antiretroviral Therapeutics*

Christine M. Hogan, MD, and Scott M. Hammer, MD

The course of HIV infection varies widely among individuals. Immunologic and genetic studies of long-term nonprogressors and exposed yet uninfected persons have helped to elucidate the mechanisms by which some persons are protected from HIV acquisition or have slow rates of disease progression. This two-part review describes what is currently known about host factors in HIV-1 infection. Studies for inclusion were identified by a systematic search of PubMed for English-language literature published from 1988 through June 2000. Abstracts of presentations at major meetings convened in 2000 were also included if appropriate. The first part of the review discussed cellular and humoral immunity to HIV infection. This second part describes genetic host factors—namely, inheritance of mutant chemokine receptors or ligands,

such as CCR5-Δ32, CCR2-V64I, stromal cell–derived factor-1 3'α, and CCR5 promoter polymorphisms, as well as HLA type—that affect susceptibility to infection and subsequent clinical course. Soluble inhibitory factors, the cytokine milieu, and concomitant infections also affect outcome. Knowledge of host responses is increasingly being applied to new therapeutic strategies, including early treatment, immune modulation, structured treatment interruptions, therapeutic vaccination, and new chemotherapeutic agents, as well as to vaccine development.

Ann Intern Med. 2001;134:978-996.

www.annals.org

For author affiliations and current addresses, see end of text.

For a glossary of terms, see end of text.

*Part 1 of this review was published in the 1 May 2001 issue.

A complex interplay of host and viral factors, many of which are only beginning to be understood, determines the course of HIV infection. The existence of long-term nonprogressors and exposed yet uninfected persons suggests that natural and acquired immunity to HIV exists and is a major determinant of clinical outcome.

This article, the second of two reviewing the role of host factors in HIV infection, discusses the role of genetic host factors—namely, inheritance of mutant chemokine receptors or ligands as well as HLA type—in susceptibility to infection with HIV and subsequent clinical course. The effects of soluble inhibitory factors, the cytokine milieu, and concomitant infections are also described (Table 1, Figure 1).

METHODS

Studies for inclusion were identified by a systematic search of PubMed for English-language literature published from 1988 through June 2000. Abstracts of presentations at major meetings convened in 2000 were also included if appropriate. The text and references in this article reflect a synthesis of the available information and an attempt to place this information in the context of the current state of the art.

The funding sources had no direct role in the preparation of this paper or in the decision to submit the paper for publication.

CHEMOKINES, CYTOKINES, AND OTHER SOLUBLE FACTORS

Chemokines

A breakthrough in our understanding of HIV pathogenesis, and thus in our understanding of host factors that can affect disease progression and susceptibility to infection, was the identification in 1996 of chemokine receptors as necessary co-receptors for HIV entry into CD4⁺ cells. Chemokines are chemoattractant substances secreted at sites of infection or injury (64). It had been known since the mid-1980s that presence of CD4 on a cell surface was necessary but not sufficient for entry of HIV into the cell. In addition, it was known that CD8 cells secrete substances that interfere with the ability of HIV to infect cells. In 1995, Cocchi and colleagues (1) identified these substances as RANTES (regulated on activation, normal T expressed and secreted); macrophage inflammatory protein-1α (MIP-1α); and MIP-1β. It was hypothesized that these substances bind to a receptor that the virus requires for cell entry.

In 1996, Feng and associates (2) isolated CXCR4 (originally referred to as “fusin”), a chemokine receptor located on T cells that T-cell-tropic (T-tropic) HIV uses as a co-receptor along with CD4. However, it was known that RANTES, MIP-1α, and MIP-1β suppressed macrophage-tropic (M-tropic) but not T-tropic virus. In the same year, several groups published results showing that the receptor for RANTES, MIP-1α, and

Table 1. Host Factors in HIV Infection*

Host Factors	Effects on HIV Transmission and Disease Progression	Reference
Cell-mediated immunity		
Cytotoxic T cells	Eliminate virions and virus-infected cells; play prominent role in initial control of viremia, slowing of disease progression, and perhaps prevention of infection	Discussed in Part 1
T-helper cell response	Preservation of this response may be vital to preservation of cytotoxic T-lymphocyte response, and its importance provides theoretic rationale for early treatment	Discussed in Part 1
Humoral immunity	Role in prevention and control of disease progression is unclear	Discussed in Part 1
Local factors		Discussed in Part 1
STDs and cytokine milieu	May upregulate HIV replication	
Mucosal cytotoxic T lymphocytes and antibodies	Role in prevention of transmission and disease progression is unclear	
Dendritic cells	Facilitate HIV infection of T cells by capturing and transporting HIV to lymph nodes and activating T cells	
Chemokine receptors		
CCR5-Δ32	Homozygosity for this deletion is associated with decreased susceptibility to infection; heterozygosity is associated with delayed progression to disease	1–21
CCR2-V64I	Heterozygosity is associated with delayed progression to disease	16–20, 22–30
CCR5 promoter polymorphisms	Several genetic polymorphisms that may affect transmission or disease progression have been identified—for example, 59029-G homozygosity is associated with slower progression, and 59356-T homozygosity is associated with increased perinatal transmission	17, 31, 32
Chemokines		
SDF-1 3'α	Homozygosity may be associated with delayed progression to disease	4, 17, 19, 24, 26, 33–39
Cytokines	Complex interplay of stimulatory and inhibitory cytokines affects HIV replication	40–49
Other soluble factors	Inhibit HIV replication in a noncytotoxic manner	44, 50–54
Other genetic factors		
HLA alleles	Certain alleles are associated with differing susceptibilities to infection and rates of disease progression	55–63

* SDF = stromal cell–derived factor; STD = sexually transmitted disease.

MIP-1β was a chemokine receptor called *CCR5* (originally referred to as “CKR-5”) that is present on macrophages, monocytes, and some T cells (3–8). Human immunodeficiency virus uses these chemokine receptors as co-receptors for entry. The interaction between the virus envelope protein gp120 and CD4 induces a conformational change that allows interaction between the virus and the chemokine receptor and ultimate fusion of the virus and host cell membrane (65–68).

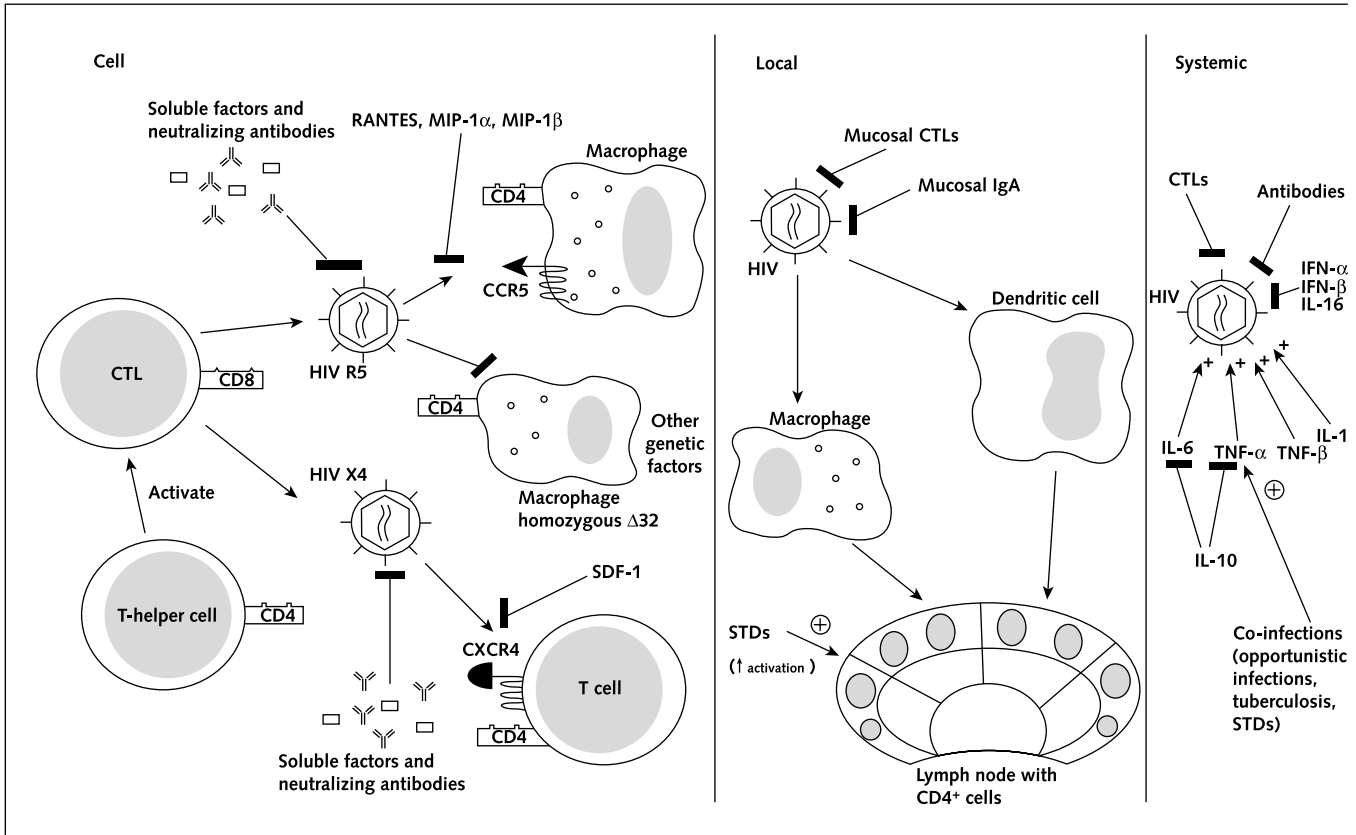
Thus, the currently held model is that M-tropic HIV strains (termed *R5 viruses*) infect macrophages, monocytes, and T cells by using the host's expression of CD4 and CCR5 as co-receptors. T-tropic HIV strains (termed *X4 viruses*) infect T cells by using CD4 and CXCR4 as co-receptors (69) (Figure 2). However, the chemokine system is complex and often redundant, and the above model does not always apply. For example, some M-tropic strains of HIV can use other co-receptors, such as CCR2 or CCR3, instead of CCR5 for entry into macrophages. In addition, syncytium-induc-

ing variants with dual tropism that can use CCR5 or CXCR4 as co-receptors have been isolated (6, 7, 70).

The host's natural ligands for these co-receptors are relevant because they may interfere with HIV entry into target cells (Table 2). CCR5 binds RANTES, MIP-1α, and MIP-1β, which are members of the β-chemokine family and are often referred to as *CCR5-using chemokines*. CXCR4 binds a member of the α-chemokine family, stromal cell–derived factor-1 (SDF-1). CCR2 binds monocyte chemotactic protein-1 (MCP-1) through MCP-5. CCR3 binds MCP-3 and MCP-4 and eotaxin 1 and 2 (64). For further information on other chemokine receptors that serve as co-receptors for HIV and simian immunodeficiency virus (SIV), see reference 92.

The ligands for the chemokine receptors can block viral entry by interfering with viral binding to the receptor or by downregulating the receptor (93). The CCR5-using chemokines—RANTES, MIP-1α, and MIP-1β—can block M-tropic strains of HIV, whereas SDF-1 blocks T-tropic strains. CD4 T cells from exposed yet

Figure 1. Schematic overview of host responses at the cellular, local, and systemic levels.



At the cellular level, CD8⁺ cytotoxic T cells (CTLs), with the help of CD4⁺ T-helper cells, lyse HIV-infected cells (discussed in part 1 of the review). Soluble factors and neutralizing antibodies inhibit viral replication. Macrophage-tropic HIV (R5) infects cells bearing CD4 and CCR5 co-receptor. T-cell-tropic HIV (X4) infects cells bearing CD4 and CXCR4 co-receptor. RANTES (regulated on activation, normal T expressed and secreted); macrophage inflammatory protein (MIP)-1α; and MIP-1β—natural ligands for the CCR5 receptor—block R5 from infecting CCR5-bearing cells. Stromal cell–derived factor (SDF)-1, the natural ligand for the CXCR4 receptor, may block X4 from infecting CXCR4-bearing cells. Macrophages from persons bearing the CCR5-Δ32 mutation and thus lacking the CCR5 co-receptor are not infected by macrophage-tropic HIV (R5). At the local level, mucosal CTLs and mucosal IgA may inhibit initial viral replication (discussed in part 1). Concomitant infections activate T cells, providing target cells for HIV to infect. Systemically, such inhibiting factors as CTLs, antibodies, interferon (IFN), and interleukin (IL)-16 are countered with such stimulating factors as tumor necrosis factor (TNF), IL-1, IL-6, and co-infections. Interleukin-10 inhibits IL-6 and TNF-α. The rectangular bars indicate sites of blockade. STD = sexually transmitted disease.

uninfected persons have been shown to produce increased levels of RANTES, MIP-1α, and MIP-1β and to suppress replication of M-tropic strains of HIV-1 (94, 95). High levels of CCR5-using chemokines have been associated with slower disease progression (96). However, other studies have found no quantitative difference in production of RANTES, MIP-1α, or MIP-1β by peripheral blood mononuclear cells of 16 discordant heterosexual couples (97) or between long-term nonprogressors and progressors (98). Some in vitro studies have even suggested that RANTES, MIP-1α, and MIP-1β may upregulate replication of HIV in macrophages and monocytes by recruiting activated target cells (99–101).

Furthermore, in vivo levels of RANTES in HIV-infected persons have been shown not to be correlated with HIV-1 viral load (102). Further research is needed to clarify the true clinical relevance and regulatory roles of these and other chemokines in HIV infection (103, 104).

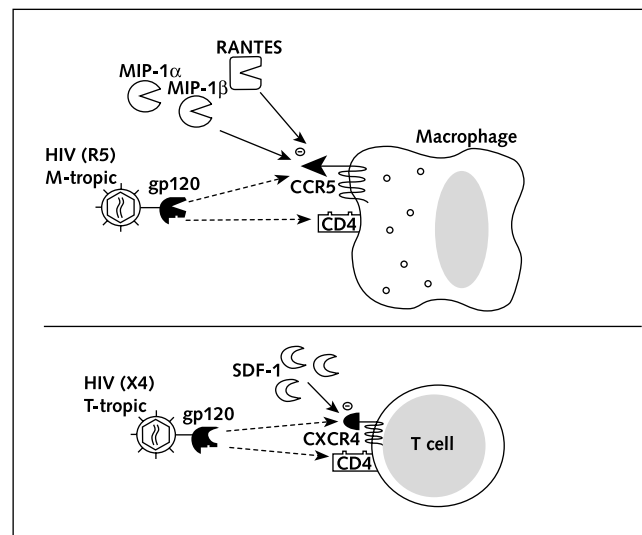
The finding that chemokine receptors are used by HIV as co-receptors for cellular entry led to the discovery of genetic host factors that can affect susceptibility to infection with HIV or the rate of progression to disease once infection is established. The best characterized of these genetic traits is the CCR5-Δ32 mutation, which was identified in 1996 (9, 10). The mutation is a 32–

base pair deletion that results in a shortened protein. In the United States, the frequency of the allele is 11% in white persons but only 1.7% in black persons. Persons who are homozygous for the deletion have decreased susceptibility to infection with HIV, although they can still be infected with T-tropic strains of the virus, which use the CXCR4 co-receptor for cell entry (9, 11, 12). Dean and colleagues (9) studied a cohort of persons with hemophilia, intravenous drug users, and men who have sex with men. Seventeen of 612 uninfected persons (compared with 0 of 1343 infected persons) were homozygous for the CCR5- Δ 32 mutation. In addition, the Chicago arm of the Multicenter AIDS Cohort Study of men who have sex with men revealed a 3.6% prevalence of homozygosity among at-risk but uninfected persons compared with a 1.4% prevalence in blood samples from random white men and 0% prevalence among HIV-infected persons (11). Reports of HIV-infected persons homozygous for the CCR5- Δ 32 mutation exist but are rare (105–108). One study of such a person demonstrated that the virus isolated from this person was homogeneous, T-tropic, and syncytium-inducing and exclusively used CXCR4 for entry (13).

With few exceptions (14, 15), most studies have found that persons heterozygous for the CCR5- Δ 32 mutation are not less susceptible to HIV infection (9, 11, 12). Data do suggest, however, that heterozygotes for the CCR5- Δ 32 mutation have delayed progression to AIDS or death (11, 12, 16–20). In the study by Dean and colleagues (9), the frequency of heterozygosity was significantly greater in long-term nonprogressors than in progressors and rapid progressors. Liu and co-workers (10) found that peripheral blood mononuclear cells of parents of uninfected homozygous persons replicated virus less efficiently. Presumably, heterozygosity limits the number of co-receptors available for HIV binding. Indeed, CCR5 density on the surface of the CD4⁺ T cell has been correlated with viral load in persons with untreated HIV-1 infection (21). Studies incorporating viral phenotype have suggested that the protective effect of CCR5- Δ 32 heterozygosity against disease progression is lost when the infecting virus is syncytium-inducing or T-tropic (109, 110), although this has not been confirmed in other studies (18). This discrepancy may be due to dual tropism of syncytium-inducing viruses.

Several other mutations in the coding region of

Figure 2. Interaction of HIV with its coreceptors.



The interaction between the virus envelope protein gp120 and CD4 induces a conformational change that allows interaction between the virus and the chemokine receptor and ultimate fusion of the virus and the host cell membrane. Macrophage-tropic (*M-tropic* or *R5*) HIV infects cells bearing CD4 and the CCR5 chemokine receptor. This interaction is blocked by natural ligands for CCR5: *RANTES* (regulated on activation, normal T expressed and secreted); macrophage inflammatory protein (*MIP*)-1 α ; and *MIP*-1 β . T-cell-tropic (*T-tropic* or *X4*) HIV infects cells bearing CD4 and the CXCR4 chemokine receptor. This interaction may be blocked by stromal cell-derived factor-1 (*SDF*-1), the natural ligand for CXCR4.

the CCR5 gene have been identified (111). A point mutation in CCR5—a T \rightarrow A substitution at position m303—encodes a truncated protein and, when found in the compound heterozygous state with Δ 32, produces a phenotype of resistance to HIV-1 primary isolates in vitro (112, 113).

Another genetic mutation that affects disease progression is the CCR2-V64I mutation, which results in normal levels of expression of the CCR2 receptor. This mutation has not been shown to affect susceptibility to infection, but HIV-infected persons heterozygous or homozygous for this mutation appear to progress to AIDS or death more slowly (16, 17, 19, 22–26); some studies, however, have not confirmed this effect on progression to disease (20, 27–29). Unlike the CCR5 mutation, which is found primarily in white persons, the frequency of the CCR2-V64I allele is 10% to 25% in both black and white persons and in all other ethnic groups studied. Studies of infected commercial sex workers in Nairobi, Kenya, suggested that the presence of the mu-

Table 2. Selected Chemokine Receptors and Ligands*

Chemokine Co-receptor	Ligand	Potential Blockers of CCR5 and CXR4	Selected References
CCR5	RANTES, MIP-1 α , MIP-1 β	AOP-RANTES, met-RANTES, 9-68 RANTES, NNY-RANTES, SCH-C, TAK-779, PRO-140	71–82
CXCR4	SDF-1	AMD 3100, T-22, met-SDF-1 β , ALX40-4C	82–91
CCR3	MCP-1, MCP-2, MCP-3, MCP-4, MCP-5		
CCR2b	MCP-3, MCP-4, eotaxin		

* MCP = monocyte chemotactic protein; MIP = macrophage inflammatory protein; RANTES = regulated on activation, normal T expressed and secreted; SDF = stromal cell–derived factor.

tation helped to explain slow progression in 21% to 46% of slow progressors (22).

It is unclear how heterozygosity for a mutant form of a chemokine receptor that most strains of HIV-1 do not use for cell entry could affect disease progression. The allele is not associated with a dysfunctional co-receptor, and the protective effect may involve cross-regulation with other co-receptors (30). It has been suggested that the CCR2-V64I mutation tracks with another mutation through linkage disequilibrium, particularly in the regulatory or promoter region of CCR5 (16, 23, 24). A polymorphism within the regulatory region of CCR5, 59653-T, is in linkage disequilibrium with the V64I mutation, but the functional significance of this finding is unclear (17, 23, 24).

A third genetic trait that may affect progression to AIDS involves SDF-1, the chief ligand for CXCR4. Stromal cell–derived factor-1 has been shown to block infection with X4-variant HIV-1 (33, 34). The mutated gene, SDF-1 3'α, involves a mutation in an untranslated region of the gene and may upregulate the synthesis of SDF-1, thus competitively inhibiting T-tropic strains of HIV from binding. Persons with HIV infection who are homozygous for this mutation have been shown to experience delayed progression to AIDS but do not exhibit decreased susceptibility to infection with HIV (17, 26, 35). In contrast, other studies have shown that SDF-1 3'α homozygosity is associated with accelerated disease progression (24, 36–38), increased viral replication (39), or no effect on disease progression (19). However, one of these studies (36) showed prolonged survival after diagnosis of AIDS, suggesting a late protective effect of homozygosity.

Several genetic polymorphisms have been identified within the CCR5 regulatory or promoter region that may affect HIV transmission or disease progression, possibly through effects on levels of CCR5 expression

(114). Persons infected with HIV who are homozygous for allele 59029-G within the CCR5 promoter regulatory region may progress to AIDS more slowly than do those who are homozygous for the 59029-A allele (31). Other promoter haplotypes may lead to more rapid disease progression (17). Homozygosity for CCR5-59356-T, a polymorphism that occurs more frequently in black persons than in white or Hispanic persons, has been strongly associated with an increased rate of perinatal HIV-1 transmission (32).

CX3CR1 is a recently described HIV co-receptor, particularly expressed in brain, whose ligand is fractalkine. Homozygosity for a specific haplotype, CX3CR1 I249 M280, has been associated with accelerated disease progression (115). Recent work has also suggested that polymorphisms in the chemokine RANTES promoter can influence the risks for HIV infection and disease progression (116). This finding may explain previously conflicting results on the protective or putative role of RANTES. Finally, data suggest that chemokine receptor gene polymorphisms may affect response to potent antiretroviral therapy (117–119).

Cytokines

The chemokines are a subset of the broader, complex network of cytokines. These polypeptides, which are secreted by cells of the immune system and other cell types (such as fibroblasts), are involved in immunoregulation. An array of cytokines, which can be stimulatory or inhibitory or both, help determine the balance of HIV replication within the host (40, 120). In vitro studies of peripheral blood mononuclear cells and lymph node mononuclear cells from HIV-infected persons indicate that these cytokines control HIV replication. For example, tumor necrosis factor-α, tumor necrosis factor-β, interleukin-1, and interleukin-6 are proinflamma-

tory cytokines whose levels are elevated in HIV-infected persons and that enhance HIV replication (41, 50). Tumor necrosis factor- α , probably the most important and potent of the HIV-inducing cytokines, activates NF- κ B, a cellular transcription factor that induces the expression of HIV (42, 43). In contrast, interferon- α , interferon- β , and interleukin-16 suppress HIV replication (121). Other cytokines, such as interleukin-2, interleukin-4, interleukin-10, transforming growth factor- β , and interferon- γ , have been shown to induce or suppress HIV expression, depending on experimental conditions (122–125). Their role *in vivo* is unclear. Important interactions occur among these cytokines. Interleukin-10 inhibits HIV replication by blocking secretion of tumor necrosis factor- α and interleukin-6 (126). In addition, the chemokine and cytokine networks may interact. For example, interleukin-2 upregulates expression of CCR1, CCR2, and CCR3, and other cytokines may affect expression of CCR5 and CXCR4. Interhost variability in the balance of these endogenous cytokines may also affect progression of HIV-related disease (44).

Patients infected with HIV may experience a burst of viremia during intercurrent illness or opportunistic infection (127). An exogenous stimulus such as an opportunistic infection can activate the immune system and thus increase the number of targets for HIV entry by increasing the number of activated CD4 cells. These opportunistic pathogens can also lead to expression of HIV-inducing cytokines, such as tumor necrosis factor- α , interleukin-6, and interleukin-1 (45). Increased viremia during co-infection with tuberculosis (46, 128) and bursts of viremia after administration of influenza vaccine or tetanus toxoid may be explained by the above factors (47–49, 129, 130). It has been postulated that immune activation due to chronic parasitic illnesses increases susceptibility to infection with HIV and accelerates progression to disease once infection is established, and thus may partially account for rapid disease progression associated with HIV in Africa (131). A recent study in Ethiopia demonstrated a decrease in HIV plasma viral load after eradication of helminthic infections (132).

Other Soluble Factors

In 1986, investigators noted that depletion of CD8 cells from peripheral blood mononuclear cells of HIV-infected patients resulted in a marked increase in viral

replication in the remaining CD4 cells. This suppression of HIV by CD8 cells was thought to be mediated at least in part by soluble factors, since suppression could occur without cell–cell contact between the CD8 effector cells and CD4 cells—that is, through a semipermeable membrane (51). One logical conclusion would be that chemokines, which are the natural ligands for the HIV co-receptors and have been shown to suppress HIV infection *in vitro*, are indeed these soluble factors. However, studies of CD8 suppressor activity suggest that RANTES, MIP-1 α , and MIP-1 β are not fully responsible for the suppressive activity mediated by this soluble factor, the specific identification of which has been elusive (44, 50, 52, 133). Controversy exists over the identification and role of noncytolytic, non-HLA-restricted CD8-mediated soluble factors in the prevention of acquisition of HIV infection and in control of disease progression (50, 52–54, 133–141).

HLA TYPE

Several studies have suggested that specific alleles of HLA loci are associated with different rates of progression (55, 56, 142, 143) and varying susceptibility to HIV infection (144–147). The class I alleles B35 and C ω 4 have consistently been associated with accelerated progression of disease (57–59). In addition, heterozygosity at all HLA class I loci appears to be protective (56, 60). In a cohort of HIV-infected white persons, long-term nonprogression in 28% to 40% of nonprogressors was ascribed to heterozygosity at all HLA class I loci, the absence of alleles B35 and C ω 4, or both (148). The alleles B57 (55, 61, 62) and B27 (55, 61, 149, 150) have most consistently been associated with long-term nonprogression, and homozygosity for HLA-B ω 4 was recently found to be associated with long-term nonprogression to AIDS (151). A study of a more strictly defined cohort of potential long-term nonprogressors (persons with stable CD4 cell counts and HIV RNA levels < 50 copies/mL after at least 2 years of untreated HIV infection, many of whom had been infected for more than 13 years) demonstrated a dramatic association between the HLA B*5701 class I allele and nonprogressive infection. Eighty-five percent of long-term nonprogressors (11 of 13) but only 9.5% of progressors (19 of 200) had this allele (63). However, one of the largest studies of associations between HLA haplotypes and

progression found that although B27 and B57 were associated with long-term nonprogression, more robust associations with long-term nonprogression were found with B14 and C8 (152).

IMPLICATIONS FOR CURRENT ANTIRETROVIRAL THERAPEUTICS

The introduction of potent antiretroviral therapy has resulted in significant decreases in morbidity and mortality among HIV-infected persons (153, 154). The ability of potent antiretroviral therapy to produce viral suppression led to the hypothesis that HIV might be eradicable within 2 to 3 years of therapy (155, 156). However, this optimism was muted when it was shown that even patients taking potent antiretroviral therapy who had undetectable viral loads for as long as 30 months harbored a latent reservoir of resting CD4⁺ T cells carrying replication-competent virus (157, 158) and that this reservoir was established very early during primary infection. Initiation of potent antiretroviral treatment during symptomatic acute seroconversion did not prevent establishment of this reservoir (159). The half-life of these cells has been estimated to be anywhere from 6 to 44 months, and the reservoir can be replenished by small bursts of viremia or persistent, unrecognized low-level replication (160–162). Thus, even if potent antiretroviral therapy could completely suppress replication, the time to eradication would be 10 to 60 years. Even more worrisome, recent studies have suggested that potent antiretroviral therapy does not completely suppress replication (160, 163) and that drug-resistant HIV-1 can be selected *in vivo* during successful drug therapy with only transient episodes of viremia (164). Thus, current therapy, while producing dramatic clinical improvement, is unlikely to eradicate the virus (165), and adjuncts to potent antiretroviral therapy that are based on knowledge of host determinants in HIV infection are being investigated. This section highlights areas of current clinical interest and is not intended to be a comprehensive review of immune-based treatment.

Given the challenge presented by the reservoir of latently infected resting T cells, one approach is to activate these cells during potent antiretroviral therapy by using interleukin-2, thus facilitating recognition and destruction of these HIV-expressing cells by effector cells of the immune system or viral-mediated cytolysis. In

a nonrandomized study, Chun and colleagues (166) showed that the size of the pool of latently infected CD4⁺ T cells in patients with HIV who received potent antiretroviral treatment and interleukin-2 was smaller than that among patients who received potent combination antiretroviral treatment alone. In a subset of patients treated with cycles of interleukin-2 in addition to antiretroviral therapy, replication-competent HIV was undetectable in peripheral blood mononuclear cells and lymph node cells, although a small proportion of cells persistently harbored proviral DNA (166). Notably, a follow-up study revealed that when these patients stopped taking potent antiretroviral treatment, plasma viral rebound and re-emergence of the reservoir of CD4⁺ T-cells with replication-competent HIV occurred within a few weeks (167). A recent randomized trial of interleukin-2 in combination with potent antiretroviral therapy conducted in Europe found that patients receiving interleukin-2 experienced higher rates of CD4 normalization but did not experience greater decreases in the size of the latent reservoir (168). Pilot studies using other activators of T cells and macrophages—such as CD3 monoclonal antibodies (OKT3); lipopolysaccharide; and other cytokines, such as GM-CSF and interleukin-12—have been described or are ongoing (169–172).

Although many approaches to immune-based therapy derived from *in vitro* data and pathogenesis studies in humans have been contemplated, the greatest clinical attention has focused on the role of interleukin-2. The clinical efficacy of this cytokine in combination with antiretroviral therapy is currently being studied in a large multinational study, the Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT), sponsored by the National Institute of Allergy and Infectious Diseases.

Other immunologic approaches to treatment address the concern that patients with undetectable viral loads while taking potent antiretroviral therapy may no longer be able to maintain a vigorous HIV-specific humoral or cellular immune response in the face of reduced antigenic stimulation. Studies have shown that HIV-specific cytotoxic T-cell lymphocyte (CTL) effector and memory responses decline during suppression of viremia with potent antiretroviral therapy (173–177). This finding provides a rationale for early treatment during acute infection, which was discussed in part 1 of this

review (178–180); autovaccination through structured treatment interruption; and therapeutic vaccination.

Autovaccination through structured treatment interruption involves brief periodic interruptions in therapy, which presumably allow viral rebound that is robust enough to stimulate the host immune response but limited enough to allow rapid suppression with reinitiation of therapy. The goal of autovaccination is that treatment might eventually be stopped because the host immune response will continue to effectively control viremia. Studies have suggested that transient increases in viral load during treatment are associated with an increase in virus-specific CTL precursors and lymphoproliferative responses (173, 181), and some patients who have interrupted treatment, particularly those with strong HIV-specific immune responses, have experienced control of viremia in the absence of antiretroviral therapy for prolonged periods (182, 183).

Encouraging preliminary results of a structured treatment interruption trial in persons who started taking potent antiretroviral therapy during acute HIV-1 infection show that treatment interruption leads to viral rebound that responds to reinitiation of therapy, that treatment interruptions are associated with augmentation of the HIV-specific T-helper cell responses and CTL responses, and that the magnitude of this augmentation increases with repeated interruptions (184). Follow-up revealed that five of eight persons treated with antiretroviral therapy during acute infection who underwent one or two supervised treatment interruptions remained free of medication and had HIV RNA levels less than 500 copies/mL a median of 6.5 months after discontinuing treatment (184). Modest improvements in cellular immune responses have also been found in chronically infected persons undergoing structured treatment interruption (185, 186). Many trials of structured treatment interruption are under way, some of which have suggested that repeated treatment interruption may lead to immunologic control of viremia in the absence of antiretroviral therapy (187–192). Concerns with this approach are potential development of resistance, “seeding” of sanctuaries during viremia, and potential increases in the reservoir of latently infected CD4 cells.

Structured treatment interruption in this context is to be differentiated from the use of structured treatment interruption in patients in whom antiretroviral therapy

has failed. The goal of the latter strategy is the reversion of drug-resistant virus to wild-type virus in the hope of improving response to an antiretroviral regimen (193–195). Another strategy for patients who respond to antiretroviral therapy is structured intermittent therapy, which involves cycling on and off antiretroviral therapy in an attempt to diminish drug toxicity and prolong effective therapy with minimal risk for resistance (196, 197).

Therapeutic vaccination involves application of exogenous antigenic stimulation to stimulate the host's waning immunity in the setting of controlled viremia (198). Before or during the transition to the era of potent antiretroviral therapy, studies of therapeutic vaccination of HIV-infected persons with inactivated HIV-1 immunogen or subunit vaccines showed improvement in HIV-specific cellular and humoral immunity but no substantial clinical benefit (199–204). In two randomized, double-blind, placebo-controlled trials of therapeutic vaccination superimposed on antiretroviral therapy (if prescribed)—one involving HIV-1 immunogen (envelope-depleted inactivated virus) (203) and one involving recombinant gp160 vaccine (204)—patients receiving the therapeutic vaccine showed improved HIV-specific T-helper activity and modestly improved CD4 cell counts compared with those not receiving the vaccine, but the rate of progression of clinical disease was not reduced. Other trials have suggested improvement in some clinical variables with therapeutic vaccination (205, 206).

Trials involving therapeutic vaccination in the setting of potent antiretroviral therapy have also shown improved HIV-specific cellular immune responses (207, 208). Trials of therapeutic vaccination in the setting of fully suppressive potent antiretroviral therapy, undertaken in the hope that the heightened cellular immune response will be able to control viremia once potent antiretroviral therapy is discontinued, are currently under way in animals and humans (209–211). In addition, delivery of HIV antigen through dendritic cells may restore anti-HIV-1 CD8⁺ T-cell responses during potent antiretroviral therapy (212, 213).

Therapeutically, intense efforts are under way to develop HIV entry inhibitors (214, 215). T-20, a synthetic peptide that inhibits infection by disrupting the HIV gp41 conformational changes associated with membrane fusion, has been shown in vivo to potently inhibit HIV

replication and represents a new class of antiviral agents that block membrane fusion and viral entry (216). Therapeutic agents that interfere with chemokine co-receptors might also block membrane fusion and viral entry. Agents that block or prevent expression of CCR5 might prove fruitful and safe for prevention of as well as therapy for HIV infection. Persons who are homozygous for the CCR5- Δ 32 mutation appear to experience no adverse health consequences related to lack of a functional CCR5 receptor. The known inhibitory effects of the ligands for CCR5—RANTES, MIP-1 α , and MIP-1 β —have led to consideration of their use as potential therapeutic agents to limit HIV entry or replication (217). However, actual use of CCR5-using chemokines themselves has potential disadvantages. These chemokines may recruit HIV-susceptible cells through chemotaxis, increase T-tropic HIV replication (71), and even increase infectivity of M-tropic viruses (218). However, development of modified or truncated RANTES molecules, such as AOP-RANTES, 9-68 RANTES, and met-RANTES, may block HIV without activating chemotaxis or proinflammatory effects and without increasing levels of T-tropic HIV (71–76).

Anti-CCR5 monoclonal antibodies are also being investigated for antiviral activity (77–79). Finally, SCH-C, a small molecular antagonist of CCR5 that is orally bioavailable and has potent *in vitro* antiretroviral activity, is another potential new therapeutic agent (80) (Table 2).

Similarly, modified ligands for the CXCR4 receptor represent another potential therapeutic approach (82, 83). The bicyclam AMD-3100 blocks HIV-1 entry through CXCR4 and inhibits binding of SDF-1 α to CXCR4 but does not itself trigger cell signaling (84–86). Other small molecule inhibitors that block T-tropic HIV-1 have been identified, such as ALX40-4C and T22 (87, 88). Unlike CCR5, CXCR4 and its ligand SDF-1 have been shown to be crucial for fetal development and survival in animals. Mice lacking CXCR4 or SDF-1 die perinatally. The CXCR4 receptor and its ligand SDF-1 appear to be involved with B-cell lymphopoiesis, bone marrow myelopoiesis, cardiac development, cerebellar development, and vascularization of the gastrointestinal tract (89, 90, 219). Clinical application of CXCR4 blockers may therefore be limited, although the effect on embryogenesis may not present a problem beyond the early stages of development.

Other areas of investigation are the development of ligands that prevent a given receptor from being expressed on a cell surface, administration of CD4 cells with decreased expression of CCR5, gene therapy to prevent receptor expression through antibodies or altered ligands, and development of pseudoviruses or vectors that express CD4 and chemokine receptors and thus could target HIV-infected cells to deliver antiviral treatment or kill HIV-infected cells (220–222). References 223 through 226 offer further review of these topics.

The potential utility of targeting CCR5 as a site of inhibition of HIV is clear, but concern has been raised that this might select for viral strains that use CXCR4 and may be more pathogenic. However, the transition from R5 to X4 viruses may occur slowly, suggesting that selection pressure suppresses the transition to use of CXCR4. Indeed, several studies have suggested that early appearance of the syncytium-inducing variants can be suppressed by immunologic mechanisms (227–229). Thus, inhibition of CCR5 will not necessarily lead to rapid emergence of highly pathogenic viruses (230). However, the X4 viruses that arise in CCR5- Δ 32 homozygotes may be accompanied by more rapid decreases in CD4 cell counts, and caution is therefore warranted (13). In addition, mouse models using N-terminal modification with RANTES have shown that HIV-1 infection can be blocked *in vivo*, but use of RANTES antagonists selected for virus that can use the CXCR4 co-receptor, suggesting that blockage of the CCR5 co-receptor alone may not be sufficient (81). Combination approaches involving two chemokine receptor blockers or a chemokine receptor blocker in addition to other fusion or entry inhibitors are being explored (82, 91).

IMPLICATIONS FOR VACCINE DEVELOPMENT

One of the key impediments to successful development of an HIV-1 vaccine is lack of knowledge of the definitive immunologic correlates of protection. However, the study of exposed yet uninfected persons and long-term nonprogressors has yielded insights into this critical question (231). Current opinion is that a successful vaccine will need to elicit strong, durable, and broadly directed CTL and neutralizing antibody responses with cross-clade activity. Efforts are under way to achieve this goal using a number of candidate vac-

cines, including recombinant envelope subunits; live virus vectors expressing HIV gene products, such as vaccinia or canarypox constructs; “prime-boost” strategies that involve live virus vectors and subunit boosters; and DNA vaccines (232–245). A wide array of formulations and delivery systems are under investigation (246–250). Ultimately, phase III studies of newer candidate vaccines will be needed to determine efficacy (251, 252).

The aim of an effective vaccine ideally would be to produce sterilizing immunity in all recipients. However, even a vaccine with a smaller but significant effect on reducing transmission or one that did not affect transmission but ameliorated disease progression (253–255) would offer substantial benefit. References 256 and 257 provide further discussion of the current status of HIV vaccine development.

SUMMARY

Research efforts during the past several years have provided insight into the complex host response to HIV exposure and infection. Specifically, immunologic and genetic studies of long-term nonprogressors and exposed yet uninfected persons have helped to elucidate the mechanisms by which some persons have slow rates of disease progression or are protected from HIV acquisition. Application of this knowledge to therapeutic strategies involving new chemotherapeutic agents, immune modulation, structured treatment interruptions, and therapeutic vaccination is ongoing. Most important, this knowledge is being used to identify the effective *in vivo* immune responses that control HIV replication in infected persons and to mimic these responses in HIV-negative persons in the hope of developing a truly effective HIV vaccine.

GLOSSARY

CCR2-V64I: A substitution of valine for isoleucine in the CCR2 receptor gene, resulting in normal levels but altered first transmembrane region of the CCR2 receptor, which has been associated with delayed progression of HIV-related illness.

CCR5: A chemokine receptor present on macrophages, monocytes, and some T cells, particularly memory T cells. Along with CD4, CCR5 acts as a co-receptor for M-tropic HIV.

CCR5-Δ32: A 32–base pair deletion in the CCR5 gene that results in a shortened and nonfunctional protein. Homozygosity for CCR5-Δ32 is associated with decreased susceptibility to HIV,

and heterozygosity is associated with delayed progression of HIV-related illness.

Chemokines: Chemoattractant cytokines that are secreted by a variety of cells to attract neutrophils, T cells, macrophages, eosinophils, and basophils to sites of inflammation, infection, or injury.

α-Chemokines: Ligands that bind to chemokine receptors of the CXC (for example, CXCR4) family and are chemotactic primarily for neutrophils, including but not limited to stromal cell–derived factor-1, the chief ligand for CXCR4.

β-Chemokines: Ligands that bind to chemokine receptors of the CC (for example, CCR5) family and are chemotactic primarily for T cells, macrophages, eosinophils, basophils, natural killer cells, and dendritic cells. This category includes RANTES (regulated on activation, normal T expressed and secreted); macrophage inflammatory protein (MIP)-1α; MIP-1β; monocyte chemoattractant protein; and eotaxin. Of these, RANTES, MIP-1α, and MIP-1β are the CCR5-using chemokines.

CXCR4: Chemokine receptor located on T cells, particularly naive T cells, which, along with CD4, acts as a co-receptor for T-tropic HIV.

Cytokines: Polypeptides secreted by cells of the immune system and other cell types, such as fibroblasts, that are involved in immunoregulation. Cytokines can be stimulatory, inhibitory, or both.

Macrophage-tropic (M-tropic) HIV: HIV variants with a non-syncytium-inducing phenotype that *in vitro* infect monocyte-derived macrophages but not established CD4⁺ T-cell lines. Also called *R5 variants* because they use the CCR5 co-receptor for entry, they tend to be the predominant variant during early infection.

Stromal cell–derived factor-1 3′α: A point mutation in the untranslated region of the SDF-1 gene that, in the homozygous state, may affect progression to AIDS.

T-cell-tropic (T-tropic) HIV: HIV variants with a syncytium-inducing phenotype that infect established CD4⁺ T-cell lines. Also called *X4 variants* because they use the CXCR4 co-receptor for entry, they tend to emerge during a later stage of HIV infection.

From Columbia University College of Physicians and Surgeons, New York, New York.

Acknowledgment: The authors thank Brian-Fred Fitzsimmons, MD, for assistance with preparation of the figures.

Grant Support: Dr. Hammer is supported by grants AI46386 and AI48013 from the National Institute of Allergy and Infectious Diseases. Dr. Hogan is supported in part by Center for AIDS Research grant 5P30AI42848-03 from the National Institute of Health and the

National Institute of Allergy and Infectious Diseases and in part by the SmithKline Beecham Development Partners Junior Faculty Award.

Requests for Single Reprints: Christine M. Hogan, MD, Division of Infectious Diseases, Columbia University, College of Physicians and Surgeons, P & S Box 82, 630 West 168th Street, New York, NY 10032; e-mail, ch358@columbia.edu.

Current Author Addresses: Drs. Hogan and Hammer: Division of Infectious Diseases, Columbia University, College of Physicians and Surgeons, P & S Box 82, 630 West 168th Street, New York, NY 10032.

References

- Cocchi F, DeVico AL, Garzino-Demo A, Arya SK, Gallo RC, Lusso P. Identification of RANTES, MIP-1 alpha, and MIP-1 beta as the major HIV-suppressive factors produced by CD8⁺ T cells. *Science*. 1995;270:1811-5. [PMID: 8525373]
- Feng Y, Broder CC, Kennedy PE, Berger EA. HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. *Science*. 1996;272:872-7. [PMID: 8629022]
- Dragic T, Litwin V, Allaway GP, Martin SR, Huang Y, Nagashima KA, et al. HIV-1 entry into CD4⁺ cells is mediated by the chemokine receptor CC-CKR-5. *Nature*. 1996;381:667-73. [PMID: 8649512]
- Alkhatib G, Combadiere C, Broder CC, Feng Y, Kennedy PE, Murphy PM, et al. CC CKR5: a RANTES, MIP-1 α , MIP-1 β receptor as a fusion cofactor for macrophage-tropic HIV-1. *Science*. 1996;272:1955-8. [PMID: 8658171]
- Deng H, Liu R, Ellmeier W, Choe S, Unutmaz D, Burkhardt M, et al. Identification of a major co-receptor for primary isolates of HIV-1. *Nature*. 1996;381:661-6. [PMID: 8649511]
- Choe H, Farzan M, Sun Y, Sullivan N, Rollins B, Ponath PD, et al. The beta-chemokine receptors CCR3 and CCR5 facilitate infection by primary HIV-1 isolates. *Cell*. 1996;85:1135-48. [PMID: 8674119]
- Doranz BJ, Rucker J, Yi Y, Smyth RJ, Samson M, Peiper SC, et al. A dual-tropic primary HIV-1 isolate that uses fusin and the beta-chemokine receptors CKR-5, CKR-3, and CKR-2b as fusion cofactors. *Cell*. 1996;85:1149-58. [PMID: 8674120]
- Samson M, Labbe O, Mollereau C, Vassart G, Parmentier M. Molecular cloning and functional expression of a new human CC-chemokine receptor gene. *Biochemistry*. 1996;35:3362-7. [PMID: 8977299]
- Dean M, Carrington M, Winkler C, Huttley GA, Smith MW, Allikmets R, et al. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. *Science*. 1996;273:1856-62. [PMID: 8791590]
- Liu R, Paxton WA, Choe S, Ceradini D, Martin SR, Horuk R, et al. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell*. 1996;86:367-77. [PMID: 8756719]
- Huang Y, Paxton WA, Wolinsky SM, Neumann AU, Zhang L, He T, et al. The role of a mutant CCR5 allele in HIV-1 transmission and disease progression. *Nat Med*. 1996;2:1240-3. [PMID: 8898752]
- Zimmerman PA, Buckler-White A, Alkhatib G, Spalding T, Kubofcik J, Combadiere C, et al. Inherited resistance to HIV-1 conferred by an inactivating mutation in CC chemokine receptor 5: studies in populations with contrasting clinical phenotypes, defined racial background, and quantified risk. *Mol Med*. 1997;3:23-36. [PMID: 9132277]
- Michael NL, Nelson JA, KewalRamani VN, Chang G, O'Brien SJ, Mascola JR, et al. Exclusive and persistent use of the entry coreceptor CXCR4 by human immunodeficiency virus type 1 from a subject homozygous for CCR5 delta32. *J Virol*. 1998;72:6040-7. [PMID: 9621067]
- Samson M, Libert F, Doranz BJ, Rucker J, Liesnard C, Farber CM, et al. Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature*. 1996;382:722-5. [PMID: 8751444]
- Hoffman TL, MacGregor RR, Burger H, Mick R, Doms RW, Collman RG. CCR5 genotypes in sexually active couples discordant for human immunodeficiency virus type 1 infection status. *J Infect Dis*. 1997;176:1093-6. [PMID: 9333175]
- Smith MW, Dean M, Carrington M, Winkler C, Huttley GA, Lomb DA, et al. Contrasting genetic influence of CCR2 and CCR5 variants on HIV-1 infection and disease progression. Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City Cohort (SFCC), ALIVE Study. *Science*. 1997;277:959-65. [PMID: 9252328]
- Martin MP, Dean M, Smith MW, Winkler C, Gerrard B, Michael NL, et al. Genetic acceleration of AIDS progression by a promoter variant of CCR5. *Science*. 1998;282:1907-11. [PMID: 9836644]
- de Roda Husman AM, Koot M, Cornelissen M, Keet IP, Brouwer M, Broersen SM, et al. Association between CCR5 genotype and the clinical course of HIV-1 infection. *Ann Intern Med*. 1997;127:882-90. [PMID: 9382366]
- Meyer L, Magierowska M, Hubert JB, Theodorou I, van Rij R, Prins M, et al. CC-chemokine receptor variants, SDF-1 polymorphism, and disease progression in 720 HIV-infected patients. SEROCO Cohort. Amsterdam Cohort Studies on AIDS [Letter]. *AIDS*. 1999;13:624-6. [PMID: 10203391]
- Ioannidis JP, O'Brien TR, Rosenberg PS, Contopoulos-Ioannidis DG, Goedert JJ. Genetic effects on HIV disease progression [Letter]. *Nat Med*. 1998;4:536. [PMID: 9585207]
- Reynes J, Portales P, Segondy M, Baillat V, André P, Réant B, et al. CD4⁺ T cell surface CCR5 density as a determining factor of virus load in persons infected with human immunodeficiency virus type 1. *J Infect Dis*. 2000;181:927-32. [PMID: 10720514]
- Anzala AO, Ball TB, Rostron T, O'Brien SJ, Plummer FA, Rowland-Jones SL. CCR2-64I allele and genotype association with delayed AIDS progression in African women. University of Nairobi Collaboration for HIV Research [Letter]. *Lancet*. 1998;351:1632-3. [PMID: 9620723]
- Kostrikis LG, Huang Y, Moore JP, Wolinsky SM, Zhang L, Guo Y, et al. A chemokine receptor CCR2 allele delays HIV-1 disease progression and is associated with a CCR5 promoter mutation. *Nat Med*. 1998;4:350-3. [PMID: 9500612]
- Mummi S, Ahuja SS, Gonzalez E, Anderson SA, Santiago EN, Stephan KT, et al. Genealogy of the CCR5 locus and chemokine system gene variants associated with altered rates of HIV-1 disease progression. *Nat Med*. 1998;4:786-93. [PMID: 9662369]
- Rizzardi GP, Morawetz RA, Vicenzi E, Ghezzi S, Poli G, Lazzarin A, et al. CCR2 polymorphism and HIV disease. Swiss HIV Cohort [Letter]. *Nat Med*. 1998;4:252-3. [PMID: 9500580]
- Hendel H, Hénon N, Lebuanez H, Lachgar A, Poncelet H, Caillat-Zucman S, et al. Distinctive effects of CCR5, CCR2, and SDF1 genetic polymorphisms in AIDS progression. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;19:381-6. [PMID: 9833747]
- Michael NL, Louie LG, Rohrbach AL, Schultz KA, Dayhoff DE, Wang CE, et al. The role of CCR5 and CCR2 polymorphisms in HIV-1 transmission and disease progression. *Nat Med*. 1997;3:1160-2. [PMID: 9334732]
- Eugen-Olsen J, Iversen AK, Benfield TL, Koppellus U, Garred P. Chemo-

- kine receptor CCR2b 64I polymorphism and its relation to CD4 T-cell counts and disease progression in a Danish cohort of HIV-infected individuals. Copenhagen AIDS cohort. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;18:110-6. [PMID: 9637575]
29. Schinkel J, Langendam MW, Coutinho RA, Krol A, Brouwer M, Schuitemaker H. No evidence for an effect of the CCR5 $\Delta 32$ ⁺ and CCR2b 64I⁺ mutations on human immunodeficiency virus (HIV)-1 disease progression among HIV-1-infected injecting drug users. *J Infect Dis*. 1999;179:825-31. [PMID: 10068577]
30. Lee B, Doranz BJ, Rana S, Yi Y, Mellado M, Frade JM, et al. Influence of the CCR2-V64I polymorphism on human immunodeficiency virus type 1 co-receptor activity and on chemokine receptor function of CCR2b, CCR3, CCR5, and CXCR4. *J Virol*. 1998;72:7450-8. [PMID: 9696841]
31. McDermott DH, Zimmerman PA, Guignard F, Kleeberger CA, Leitman SF, Murphy PM. CCR5 promoter polymorphism and HIV-1 disease progression. Multicenter AIDS Cohort Study (MACS). *Lancet*. 1998;352:866-70. [PMID: 9742978]
32. Kostrikis L, Neumann A, Thomson B, Korber BT, McHardy P, Karanikolas R, et al. A polymorphism in the regulatory region of the CC-chemokine receptor 5 gene influences perinatal transmission of human immunodeficiency virus type 1 to African-American infants. *J Virol*. 1999;73:10264-71. [PMID: 10559343]
33. Bleul CC, Farzan M, Choe H, Parolin C, Clark-Lewis I, Sodroski J, et al. The lymphocyte chemoattractant SDF-1 is a ligand for LESTR/fusin and blocks HIV-1 entry. *Nature*. 1996;382:829-33. [PMID: 8752280]
34. Oberlin E, Amara A, Bachelier F, Bessia C, Virelizier JL, Arenzana-Seisdedos F, et al. The CXC chemokine SDF-1 is the ligand for LESTR/fusin and prevents infection by T-cell-line-adapted HIV-1. *Nature*. 1996;382:833-5. [PMID: 8752281]
35. Winkler C, Modi W, Smith MW, Nelson GW, Wu X, Carrington M, et al. Genetic restriction of AIDS pathogenesis by an SDF-1 chemokine gene variant. ALIVE Study, Hemophilia Growth and Development Study (HGDS), Multicenter AIDS Cohort Study (MACS), Multicenter Hemophilia Cohort Study (MHCS), San Francisco City Cohort (SFCC). *Science*. 1998;279:389-93. [PMID: 9430590]
36. van Rij R, Broersen S, Goudsmit J, Coutinho R, Schuitemaker H. The role of a stromal cell-derived factor-1 chemokine gene variant in the clinical course of HIV-1 infection. *AIDS*. 1998;12:F85-90. [PMID: 9662191]
37. Lathey J, Tierney C, Chang S, D'Aquila R, Hammer S, Katzenstein D. Homozygous mutations in 3'A SDF-1 are associated with more rapid disease progression. ACTG 175 Genotype Team [Abstract]. In: 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, California, 30 January–2 February 2000. Alexandria, VA: Foundation for Retrovirology and Human Health; 2000. Abstract no. 853.
38. Brambilla A, Villa C, Rizzardi G, Veglia F, Ghezzi S, Lazzarin A, et al. Shorter survival of SDF1-3'A/3'A homozygotes linked to CD4⁺ T cell decrease in advanced human immunodeficiency virus type 1 infection. *J Infect Dis*. 2000;182:311-5. [PMID: 10882614]
39. Balotta C, Bagnarelli P, Corvasce S, Mazzucchelli R, Colombo MC, Pagnano L, et al. Identification of two distinct subsets of long-term nonprogressors with divergent viral activity by stromal-derived factor 1 chemokine gene polymorphism analysis. *J Infect Dis*. 1999;180:285-9. [PMID: 10395841]
40. Vicenzi E, Biswas P, Mengozzi M, Poli G. Role of pro-inflammatory cytokines and beta-chemokines in controlling HIV replication. *J Leukoc Biol*. 1997;62:34-40. [PMID: 9225990]
41. Folks TM, Justement J, Kinter A, Dinarello CA, Fauci AS. Cytokine-induced expression of HIV-1 in a chronically infected promonocyte cell line. *Science*. 1987;238:800-2. [PMID: 3313729]
42. Duh EJ, Maury WJ, Folks TM, Fauci AS, Rabson AB. Tumor necrosis factor alpha activates human immunodeficiency virus type 1 through induction of nuclear factor binding to the NF-kappa B sites in the long terminal repeat. *Proc Natl Acad Sci U S A*. 1989;86:5974-8. [PMID: 2762307]
43. Osborn L, Kunkel S, Nabel GJ. Tumor necrosis factor alpha and interleukin 1 stimulate the human immunodeficiency virus enhancer by activation of the nuclear factor kappa B. *Proc Natl Acad Sci U S A*. 1989;86:2336-40. [PMID: 2494664]
44. Kinter AL, Ostrowski M, Goletti D, Oliva A, Weissman D, Gantt K, et al. HIV replication in CD4⁺ T cells of HIV-infected individuals is regulated by a balance between the viral suppressive effects of endogenous beta-chemokines and the viral inductive effects of other endogenous cytokines. *Proc Natl Acad Sci U S A*. 1996;93:14076-81. [PMID: 8943063]
45. Wahl SM, Greenwell-Wild T, Peng G, Hale-Donze H, Orenstein JM. Co-infection with opportunistic pathogens promotes human immunodeficiency virus type 1 infection in macrophages. *J Infect Dis*. 1999;179(Suppl 3):S457-60. [PMID: 10099119]
46. Goletti D, Weissman D, Jackson R, Graham N, Vlahov D, Klein R, et al. Effect of *Mycobacterium tuberculosis* on HIV replication. Role of immune activation. *J Immunol*. 1996;157:1271-8. [PMID: 8757635]
47. Staprans SI, Hamilton BL, Follansbee SE, Elbeik T, Barbosa P, Grant RM, et al. Activation of virus replication after vaccination of HIV-1-infected individuals. *J Exp Med*. 1995;182:1727-37. [PMID: 7500017]
48. Stanley S, Ostrowski MA, Justement JS, Gantt K, Hedayati S, Mannix M, et al. Effect of immunization with a common recall antigen on viral expression in patients infected with human immunodeficiency virus type 1. *N Engl J Med*. 1996;334:1222-30. [PMID: 8606717]
49. Kroon FP, Beersma MF, Kroes AC, Groeneveld PH, van Dissel JT. Vaccination and HIV-1 replication during highly active antiretroviral therapy [Letter]. *AIDS*. 1999;13:135-6. [PMID: 10207556]
50. Moriuchi H, Moriuchi M, Combadiere C, Murphy PM, Fauci AS. CD8⁺ T-cell-derived soluble factor(s), but not β -chemokines RANTES, MIP-1 α , and MIP-1 β , suppress HIV-1 replication in monocyte/macrophages. *Proc Natl Acad Sci U S A*. 1996;93:15341-5. [PMID: 8986813]
51. Walker CM, Moody DJ, Sittes DP, Levy JA. CD8⁺ lymphocytes can control HIV infection in vitro by suppressing virus replication. *Science*. 1986;234:1563-6. [PMID: 2431484]
52. Stranford S, Skurnick J, Louria D, Osmond D, Chang SY, Sninsky J, et al. Lack of infection in HIV-exposed individuals is associated with a strong CD8⁽⁺⁾ cell noncytotoxic anti-HIV response. *Proc Natl Acad Sci U S A*. 1999;96:1030-5. [PMID: 9927688]
53. Walker CM, Erickson AL, Hsueh FC, Levy JA. Inhibition of human immunodeficiency virus replication in acutely infected CD4⁺ cells by CD8⁺ cells involves a noncytotoxic mechanism. *J Virol*. 1991;65:5921-7. [PMID: 1920621]
54. Yang OO, Kalams SA, Trocha A, Cao H, Luster A, Johnson RP, et al. Suppression of human immunodeficiency virus type 1 replication by CD8⁺ cells: evidence for HLA class I-restricted triggering of cytolytic and noncytolytic mechanisms. *J Virol*. 1997;71:3120-8. [PMID: 9060675]
55. Kaslow RA, Carrington M, Apple R, Park L, Muñoz A, Saah AJ, et al. Influence of combinations of human major histocompatibility complex genes on the course of HIV-1 infection. *Nat Med*. 1996;2:405-11. [PMID: 8597949]
56. Keet IP, Tang J, Klein MR, LeBlanc S, Enger C, Rivers C, et al. Consistent associations of HLA class I and II and transporter gene products with progression of human immunodeficiency virus type 1 infection in homosexual men. *J Infect Dis*. 1999;180:299-309. [PMID: 10395843]
57. Tomiyama H, Miwa K, Shiga H, Moore YI, Oka S, Iwamoto A, et al. Evidence of presentation of multiple HIV-1 cytotoxic T lymphocyte epitopes by HLA-B*3501 molecules that are associated with the accelerated progression of

- AIDS. *J Immunol.* 1997;158:5026-34. [PMID: 9144523]
58. Jeannot M, Sztajzel R, Carpentier N, Hirschel B, Tiercy JM. HLA antigens are risk factors for development of AIDS. *J Acquir Immune Defic Syndr.* 1989; 2:28-32. [PMID: 2783969]
59. Itescu S, Mathur-Wagh U, Skovron ML, Brancato LJ, Marmor M, Zeleniuch-Jacquotte A, et al. HLA-B35 is associated with accelerated progression to AIDS. *J Acquir Immune Defic Syndr.* 1992;5:37-45. [PMID: 1738086]
60. Tang J, Costello C, Keet IP, Rivers C, Leblanc S, Karita E, et al. HLA class I homozygosity accelerates disease progression in human immunodeficiency virus type 1 infection. *AIDS Res Hum Retroviruses.* 1999;15:317-24. [PMID: 10082114]
61. Klein MR, van der Burg SH, Hovenkamp E, Holwerda AM, Drijfhout JW, Melief CJ, et al. Characterization of HLA-B57-restricted human immunodeficiency virus type 1 Gag- and RT-specific cytotoxic T lymphocyte responses. *J Gen Virol.* 1998;79(Pt 9):2191-201. [PMID: 9747728]
62. Goulder PJ, Bunce M, Krausa P, McIntyre K, Crowley S, Morgan B, et al. Novel, cross-restricted, conserved, and immunodominant cytotoxic T lymphocyte epitopes in slow progressors in HIV type 1 infection. *AIDS Res Hum Retroviruses.* 1996;12:1691-8. [PMID: 8959245]
63. Migueles SA, Sabbaghian MS, Shupert W, Bettinotti MP, Marincola FM, Martino L, et al. HLA B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long term nonprogressors. *Proc Natl Acad Sci U S A.* 2000;97:2709-14. [PMID: 10694578]
64. Luster AD. Chemokines—chemotactic cytokines that mediate inflammation. *N Engl J Med.* 1998;338:436-45. [PMID: 9459648]
65. Rizzuto CD, Wyatt R, Hernández-Ramos N, Sun Y, Kwong PD, Hendrickson WA, et al. A conserved HIV gp120 glycoprotein structure involved in chemokine receptor binding. *Science.* 1998;280:1949-53. [PMID: 9632396]
66. Wyatt R, Sodroski J. The HIV-1 envelope glycoproteins: fusogens, antigens, and immunogens. *Science.* 1998;280:1884-8. [PMID: 9632381]
67. Kwong PD, Wyatt R, Robinson J, Sweet RW, Sodroski J, Hendrickson WA. Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody. *Nature.* 1998;393:648-59. [PMID: 9641677]
68. Wu L, Gerard NP, Wyatt R, Choe H, Parolin C, Ruffing N, et al. CD4-induced interaction of primary HIV-1 gp120 glycoproteins with the chemokine receptor CCR-5. *Nature.* 1996;384:179-83. [PMID: 8906795]
69. Berger EA, Doms RW, Fenyö EM, Korber BT, Littman DR, Moore JP, et al. A new classification for HIV-1 [Letter]. *Nature.* 1998;391:240. [PMID: 9440686]
70. Simmons G, Wilkinson D, Reeves JD, Dittmar MT, Beddows S, Weber J, et al. Primary, syncytium-inducing human immunodeficiency virus type 1 isolates are dual-tropic and most can use either Lestr or CCR5 as coreceptors for virus entry. *J Virol.* 1996;70:8355-60. [PMID: 8970955]
71. Kinter A, Catanzaro A, Monaco J, Ruiz M, Justement J, Moir S, et al. CC-chemokines enhance the replication of T-tropic strains of HIV-1 in CD4⁽⁺⁾ T cells: role of signal transduction. *Proc Natl Acad Sci U S A.* 1998;95:11880-5. [PMID: 9751759]
72. Simmons G, Clapham P, Picard L, Offord RE, Rosenkilde MM, Schwartz TW, et al. Potent inhibition of HIV-1 infectivity in macrophages and lymphocytes by a novel CCR5 antagonist. *Science.* 1997;276:276-9. [PMID: 9092481]
73. Arenzana-Seisdedos F, Virelizier JL, Rousset D, Clark-Lewis I, Loetscher P, Moser B, et al. HIV blocked by chemokine antagonist [Letter]. *Nature.* 1996; 383:400. [PMID: 8837769]
74. Ylisastigui L, Vizzavona J, Drakopoulou E, Paindavoine P, Calvo CF, Parmentier M, et al. Synthetic full-length and truncated RANTES inhibit HIV-1 infection of primary macrophages. *AIDS.* 1998;12:977-84. [PMID: 9662193]
75. Proudfoot A, Power C, Hoogewerf A, Montjovent MO, Borlat F, Offord RE, et al. Extension of recombinant human RANTES by the retention of the initiating methionine produces a potent antagonist. *J Biol Chem.* 1996;271: 2599-603. [PMID: 8576227]
76. Gong JH, Ugucioni M, Dewald B, Baggolini M, Clark-Lewis I. RANTES and MCP-3 antagonists bind multiple chemokine receptors. *J Biol Chem.* 1996; 271:10521-7. [PMID: 8631850]
77. Olson WC, Rabut GE, Nagashima KA, Tran DN, Anselma DJ, Monard SP, et al. Differential inhibition of human immunodeficiency virus type 1 fusion, gp120 binding, and CC-chemokine activity by monoclonal antibodies to CCR5. *J Virol.* 1999;73:4145-55. [PMID: 10196311]
78. Wu L, Paxton W, Kassam N, Ruffing N, Rottman JB, Sullivan N, et al. CCR5 levels and expression pattern correlate with infectability by macrophage-tropic HIV-1, in vitro. *J Exp Med.* 1997;185:1681-91. [PMID: 9151905]
79. Trkola A, Ketas TJ, Nagashima K, Zhao L, Cilliers T, Morris L, et al. Potent, broad-spectrum inhibition of human immunodeficiency virus type 1 by the CCR5 monoclonal antibody PRO140. *J Virol.* 2001;75:579-88. [PMID 11134270]
80. Baroudy B. A small molecule antagonist of CCR5 that effectively inhibits HIV-1 potential as a novel antiretroviral agent [Abstract]. In: Program and Abstracts of the 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, California, 30 January–2 February 2000. Alexandria, VA: Foundation for Retrovirology and Human Health; 2000. Abstract no. S17.
81. Mosier DE, Picchio GR, Gulizia RJ, Sabbe R, Poignard P, Picard L, et al. Highly potent RANTES analogues either prevent CCR5-using human immunodeficiency virus type 1 infection in vivo or rapidly select for CXCR4-using variants. *J Virol.* 1999;73:3544-50. [PMID: 10196243]
82. Rusconi S, LaSeta Catamancio S, Citterio P, Bulgheroni E, Croce F, Herrmann S, et al. Combination of CCR5 and CXCR4 inhibitors in therapy of human immunodeficiency virus type 1 infections: in vitro studies of mixed virus infection. *J Virol.* 2000;74:9328-32. [PMID: 10982382]
83. Rusconi S, Merrill D, LaSeta Catamancio S, Citterio P, Bulgheroni E, Croce F, et al. In vitro inhibition of HIV-1 by Met-SDF-1beta alone or in combination with antiretroviral drugs. *Antivir Ther.* 2000;5:199-204. [PMID: 11075940]
84. Donzella GA, Schols D, Lin SW, Esté JA, Nagashima K, Maddon PJ, et al. AMD3100, a small molecule inhibitor of HIV-1 entry via the CXCR4 co-receptor. *Nat Med.* 1998;4:72-7. [PMID: 9427609]
85. Schols D, Esté JA, Henson G, De Clercq E. Bicyclams, a class of potent anti-HIV agents, are targeted at the HIV coreceptor fusin/CXCR-4. *Antiviral Res.* 1997;35:147-56. [PMID: 9298754]
86. Schols D, Struyf S, Van Damme J, Esté JA, Henson G, De Clercq E. Inhibition of T-tropic HIV strains by selective antagonization of the chemokine receptor CXCR4. *J Exp Med.* 1997;186:1383-8. [PMID: 9334378]
87. Murakami T, Nakajima T, Koyanagi Y, Tachibana K, Fujii N, Tamamura H, et al. A small molecule CXCR4 inhibitor that blocks T cell line-tropic HIV-1 infection. *J Exp Med.* 1997;186:1389-93. [PMID: 9334379]
88. Doranz BJ, Grovit-Ferbas K, Sharron MP, Mao SH, Goetz MB, Daar ES, et al. A small-molecule inhibitor directed against the chemokine receptor CXCR4 prevents its use as an HIV-1 coreceptor. *J Exp Med.* 1997;186:1395-400. [PMID: 9334380]
89. Zou YR, Kottmann AH, Kuroda M, Taniuchi I, Littman DR. Function of the chemokine receptor CXCR4 in haematopoiesis and in cerebellar development. *Nature.* 1998;393:595-9. [PMID: 9634238]
90. Tachibana K, Hirota S, Iizasa H, Yoshida H, Kawabata K, Kataoka Y, et al. The chemokine receptor CXCR4 is essential for vascularization of the gastrointestinal tract. *Nature.* 1998;393:591-4. [PMID: 9634237]
91. Tremblay C, Kollmann C, Giguel F, Chou TC, Hirsch MS. Strong in vitro synergy between the fusion inhibitor T-20 and the CXCR4 blocker AMD-3100.

- J Acquir Immune Defic Syndr 2000;25:99-102. [PMID: 11103038]
92. Hoffman TL, Doms RW. Chemokines and coreceptors in HIV/SIV-host interactions. *AIDS*. 1998;12(Suppl A):S17-26. [PMID: 9632980]
93. Amara A, Gall SL, Schwartz O, Salamerio J, Montes M, Loetscher P, et al. HIV coreceptor downregulation as antiviral principle: SDF-1 α -dependent internalization of the chemokine receptor CXCR4 contributes to inhibition of HIV replication. *J Exp Med*. 1997;186:139-46. [PMID: 9207008]
94. Paxton WA, Martin SR, Tse D, O'Brien TR, Skurnick J, VanDevanter N, et al. Relative resistance to HIV-1 infection of CD4 lymphocytes from persons who remain uninfected despite multiple high-risk sexual exposure. *Nat Med*. 1996;2:412-7. [PMID: 8597950]
95. Furci L, Scarlatti G, Burastero S, Tambussi G, Colognesi C, Quillent C, et al. Antigen-driven C-C chemokine-mediated HIV-1 suppression by CD4⁽⁺⁾ T cells from exposed uninfected individuals expressing the wild-type CCR-5 allele. *J Exp Med*. 1997;186:455-60. [PMID: 9236198]
96. Ullum H, Cozzi Lepri A, Victor J, Aladdin H, Phillips AN, Gerstoft J, et al. Production of beta-chemokines in human immunodeficiency virus (HIV) infection: evidence that high levels of macrophage inflammatory protein-1 β are associated with a decreased risk of HIV disease progression. *J Infect Dis*. 1998;177:331-6. [PMID: 9466518]
97. Mazzoli S, Trabattoni D, Lo Caputo S, Piconi S, Blé C, Meacci F, et al. HIV-specific mucosal and cellular immunity in HIV-seronegative partners of HIV-seropositive individuals. *Nat Med*. 1997;3:1250-7. [PMID: 9359700]
98. McKenzie SW, Dallalio G, North M, Frame P, Means RT Jr. Serum chemokine levels in patients with non-progressing HIV infection. *AIDS*. 1996;10:F29-33. [PMID: 8853724]
99. Schmidtayerova H, Sherry B, Bukrinsky M. Chemokines and HIV replication [Letter]. *Nature*. 1996;382:767. [PMID: 8752270]
100. Schmidtayerova H, Nottet HS, Nuovo G, Raabe T, Flanagan CR, Dubrovsky L, et al. Human immunodeficiency virus type 1 infection alters chemokine beta peptide expression in human monocytes: implications for recruitment of leukocytes into brain and lymph nodes. *Proc Natl Acad Sci U S A*. 1996;93:700-4. [PMID: 8570619]
101. Canque B, Rosenzweig M, Gey A, Tartour E, Fridman WH, Gluckman JC. Macrophage inflammatory protein-1 α is induced by human immunodeficiency virus infection of monocyte-derived macrophages. *Blood*. 1996;87:2011-9. [PMID: 8634452]
102. Li Q, Zupancic M, Zhang ZQ, Wong JK, Polis M, Feinberg M, et al. The levels of RANTES expression and HIV-1 replication in the lymphoid tissues of HIV-1-infected acute and chronic patients [Abstract]. In: Program and Abstracts of the 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, California, 30 January–2 February 2000. Alexandria, VA: Foundation for Retrovirology and Human Health; 2000. Abstract no. 393.
103. Pal R, Garzino-Demo A, Markham PD, Burns J, Brown M, Gallo R, et al. Inhibition of HIV-1 infection by the beta-chemokine MDC. *Science*. 1997;278:695-8. [PMID: 9381181]
104. Lee B, Rucker J, Doms RW, Tsang M, Hu X, Dietz M, et al. B-chemokine MDC and HIV-1 infection. *Science (Technical Comments)*. 1998;281:487. Available at www.sciencemag.org/cgi/content/full/281/5376/487a. Accessed 30 December 1999.
105. Balotta C, Bagnarelli P, Violin M, Ridolfo AL, Zhou D, Berlusconi A, et al. Homozygous Δ 32 deletion of the CCR-5 chemokine receptor gene in an HIV-1-infected patient. *AIDS*. 1997;11:F67-71. [PMID: 9256936]
106. Biti R, Ffrench R, Young J, Bennetts B, Stewart G, Liang T. HIV-1 infection in an individual homozygous for the CCR5 deletion allele [Letter]. *Nat Med*. 1997;3:252-3. [PMID: 9055842]
107. O'Brien TR, Winkler C, Dean M, Nelson JA, Carrington M, Michael N, et al. HIV-1 infection in a man homozygous for CCR5 delta 32 [Letter]. *Lancet*. 1997;349:1219. [PMID: 9130945]
108. Theodorou I, Meyer L, Magierowska M, Katlama C, Rouzioux C. HIV-1 infection in an individual homozygous for CCR5 delta 32. Seroco Study Group [Letter]. *Lancet*. 1997;349:1219-20. [PMID: 9130946]
109. Michael NL, Chang G, Louie LG, Mascola JR, Dondero D, Bix DL, et al. The role of viral phenotype and CCR-5 gene defects in HIV-1 transmission and disease progression. *Nat Med*. 1997;3:338-40. [PMID: 9055864]
110. Schønning K, Joost M, Gram G, Machuca R, Nielsen C, Nielsen J, et al. Chemokine receptor polymorphism and autologous neutralizing antibody response in long-term HIV-1 infection. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;18:195-202. [PMID: 9665495]
111. Carrington M, Kissner T, Gerrard B, Ivanov S, O'Brien SJ, Dean M. Novel alleles of the chemokine-receptor gene CCR5. *Am J Hum Genet*. 1997;61:1261-7. [PMID: 9399903]
112. Quillent C, Oberlin E, Braun J, Rousset D, Gonzalez-Canali G, Métais P, et al. HIV-1-resistance phenotype conferred by combination of two separate inherited mutations of CCR5 gene. *Lancet*. 1998;351:14-8. [PMID: 9433423]
113. Garred P. Chemokine-receptor polymorphisms: clarity or confusion for HIV-1 prognosis? *Lancet*. 1998;351:2-3. [PMID: 9433416]
114. Mummidi S, Ahuja SS, McDaniel BL, Ahuja SK. The human CC chemokine receptor 5 (CCR5) gene. Multiple transcripts with 5'-end heterogeneity, dual promoter usage, and evidence for polymorphisms within the regulatory regions and noncoding exons. *J Biol Chem*. 1997;272:30662-71. [PMID: 9388201]
115. Faure S, Meyer L, Costagliola D, Vaneensberghe C, Genin E, Autran B, et al. Rapid progression to AIDS in HIV⁺ individuals with a structural variant of the chemokine receptor CX3CR1. *Science*. 2000;287:2274-7. [PMID: 10731151]
116. McDermott D, Beecroft MJ, Kleeberger C, Al-Sharif F, Ollier W, Zimmerman P, et al. Chemokine RANTES promoter polymorphism affects risk of both HIV infection and disease progression in the Multicenter AIDS Cohort Study. *AIDS*. 2000;14:2671-8. [PMID: 11125885]
117. O'Brien TR, McDermott DH, Ioannidis JP, Carrington M, Murphy PM, Havlir DV, et al. Effect of chemokine receptor gene polymorphisms on the response to potent antiretroviral therapy. *AIDS*. 2000;14:821-6. [PMID: 10839590]
118. Guerin S, Meyer L, Theodorou I, Boufassa F, Magierowska M, Goujard C, et al. CCR5-delta 32 deletion and response to highly active antiretroviral therapy in HIV-1-infected patients. *AIDS*. 2000;14:2788-90. [PMID: 11125899]
119. Workman C, Whittaker W, Forrester J, Dyer W, Sullivan J. Association of the CCR5 Δ 32 mutation with improved response to antiretroviral therapy commenced in primary HIV infection [Abstract]. In: 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, California, 30 January–2 February 2000. Alexandria, VA: Foundation for Retrovirology and Human Health; 2000. Abstract no. 570.
120. Aggarwal BB, Puri RK, eds. *Human Cytokines: Their Role in Disease and Therapy*. Cambridge, MA: Blackwell Scientific; 1995.
121. Baier M, Werner A, Bannert N, Metzner K, Kurth R. HIV suppression by interleukin-16 [Letter]. *Nature*. 1995;378:563. [PMID: 8524386]
122. Kinter AL, Poli G, Fox L, Hardy E, Fauci A. HIV replication in IL-2-stimulated peripheral blood mononuclear cells is driven in an autocrine/paracrine manner by endogenous cytokines. *J Immunol*. 1995;154:2448-59. [PMID: 7868911]
123. Valentin A, Lu W, Rosati M, Schneider R, Albert J, Karlsson A, et al. Dual effect of interleukin 4 on HIV-1 expression: implications for viral phenotypic switch and disease progression. *Proc Natl Acad Sci U S A*. 1998;95:8886-91. [PMID: 9671774]
124. Weissman D, Poli G, Fauci AS. IL-10 synergizes with multiple cytokines in enhancing HIV production in cells of monocytic lineage. *J Acquir Immune Defic*

- Syndr Hum Retrovirol. 1995;9:442-9. [PMID: 7627621]
125. Poli G, Kinter AL, Justement JS, Bressler P, Kehrl JH, Fauci AS. Transforming growth factor beta suppresses human immunodeficiency virus expression and replication in infected cells of the monocyte/macrophage lineage. *J Exp Med*. 1991;173:589-97. [PMID: 1705278]
126. Weissman D, Poli G, Fauci AS. Interleukin 10 blocks HIV replication in macrophages by inhibiting the autocrine loop of tumor necrosis factor alpha and interleukin 6 induction of virus. *AIDS Res Hum Retroviruses*. 1994;10:1199-206. [PMID: 7848677]
127. Claydon EJ, Bennett J, Gor D, Forster SM. Transient elevation of serum HIV antigen levels associated with intercurrent infection [Letter]. *AIDS*. 1991;5:113-4. [PMID: 1905552]
128. Perriens JH, Mukadi Y, Nunn P. Tuberculosis and HIV infection: implications for Africa. *AIDS*. 1991;5(Suppl 1):S127-33. [PMID: 1669909]
129. Ho DD. HIV-1 viraemia and influenza [Letter]. *Lancet*. 1992;339:1549. [PMID: 1351231]
130. Janoff EN, Tasker SA, Stevenson M, Rubins JB, O'Brien J, Utz G, et al. Immune activation and virologic response to immunization in recent HIV type 1 seroconverters. *AIDS Res Hum Retroviruses*. 1999;15:837-45. [PMID: 10381172]
131. Bentwich Z, Kalinkovich A, Weisman Z. Immune activation is a dominant factor in the pathogenesis of African AIDS. *Immunol Today*. 1995;16:187-91. [PMID: 7734046]
132. Wolday D, Maayan S, Mariam ZG, Britton S, Landay A, Bentwich Z. Eradication of helminthic infection decreases HIV plasma viral load in dually infected people [Abstract]. In: 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, California, 30 January–2 February 2000. Alexandria, VA: Foundation for Retrovirology and Human Health; 2000. Abstract no. 157.
133. Barker TD, Weissman D, Daucher JA, Roche KM, Fauci AS. Identification of multiple and distinct CD8⁺ T cell suppressor activities: dichotomy between infected and uninfected individuals, evolution with progression of disease, and sensitivity to gamma irradiation. *J Immunol*. 1996;156:4476-83. [PMID: 8666823]
134. Levy JA, Mackewicz CE, Barker E. Controlling HIV pathogenesis: the role of the noncytotoxic anti-HIV response of CD8⁺ T cells. *Immunol Today*. 1996;17:217-24. [PMID: 8991383]
135. Mackewicz CE, Yang LC, Lifson JD, Levy JA. Non-cytolytic CD8 T-cell anti-HIV responses in primary HIV-1 infection. *Lancet*. 1994;344:1671-3. [PMID: 7996961]
136. Mackewicz CE, Ortega HW, Levy JA. CD8⁺ cell anti-HIV activity correlates with the clinical state of the infected individual. *J Clin Invest*. 1991;87:1462-6. [PMID: 1707063]
137. Landay AL, Mackewicz CE, Levy JA. An activated CD8⁺ T cell phenotype correlates with anti-HIV activity and asymptomatic clinical status. *Clin Immunol Immunopathol*. 1993;69:106-16. [PMID: 8403538]
138. Barker E, Mackewicz CE, Reyes-Terán G, Sato A, Stranford SA, Fujimura SH, et al. Virological and immunological features of long-term human immunodeficiency virus-infected individuals who have remained asymptomatic compared with those who have progressed to acquired immunodeficiency syndrome. *Blood*. 1998;92:3105-14. [PMID: 9787145]
139. Kootstra NA, Miedema F, Schuitemaker H. Analysis of CD8⁺ T lymphocyte-mediated nonlytic suppression of autologous and heterologous primary human immunodeficiency virus type 1 isolates. *AIDS Res Hum Retroviruses*. 1997;13:685-93. [PMID: 9168237]
140. Furci L, Loverro P, Lopalco L, Sinnone M, Lazzarin A, Lusso P. Nonlytic suppressive activity against different biological variants of HIV-1 by CD8⁺ T lymphocytes from exposed uninfected individuals [Abstract]. In: 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, California, 30 January–2 February 2000. Alexandria, VA: Foundation for Retrovirology and Human Health; 2000. Abstract no. 159.
141. Rösok B, Voltersvik P, Larsson BM, Albert J, Brinchmann JE, Asjö B. CD8⁺ T cells from HIV type 1-seronegative individuals suppress virus replication in acutely infected cells. *AIDS Res Hum Retroviruses*. 1997;13:79-85. [PMID: 8989430]
142. Itescu S, Rose S, Dwyer E, Winchester R. Certain HLA-DR5 and -DR6 major histocompatibility complex class II alleles are associated with a CD8 lymphocytic host response to human immunodeficiency virus type 1 characterized by low lymphocyte viral strain heterogeneity and slow disease progression. *Proc Natl Acad Sci U S A*. 1994;91:11472-6. [PMID: 7972086]
143. Kroner BL, Goedert JJ, Blattner WA, Wilson SE, Carrington MN, Mann DL. Concordance of human leukocyte antigen haplotype-sharing, CD4 decline and AIDS in hemophilic siblings. Multicenter Hemophilia Cohort and Hemophilia Growth and Development Studies. *AIDS*. 1995;9:275-80. [PMID: 7755916]
144. Plummer FA, Ball TB, Kimani J, Fowke KR. Resistance to HIV-1 infection among highly exposed sex workers in Nairobi: what mediates protection and why does it develop? *Immunol Lett*. 1999;66:27-34. [PMID: 10203031]
145. Rowland-Jones SL, Dong T, Fowke KR, Kimani J, Krausa P, Newell H, et al. Cytotoxic T cell responses to multiple conserved HIV epitopes in HIV-resistant prostitutes in Nairobi. *J Clin Invest*. 1998;102:1758-65. [PMID: 9802890]
146. Kaul R, Trabattoni D, Bwayo JJ, Arienti D, Zagliani A, Mwangi FM, et al. HIV-1-specific mucosal IgA in a cohort of HIV-1-resistant Kenyan sex workers. *AIDS*. 1999;13:23-9. [PMID: 10207541]
147. Hill AV. HIV and HLA: confusion or complexity? *Nat Med*. 1996;2:395-6. [PMID: 8597943]
148. Carrington M, Nelson GW, Martin MP, Kissner T, Vlahov D, Goedert JJ, et al. HLA and HIV-1: heterozygote advantage and B*35-Cw*04 disadvantage. *Science*. 1999;283:1748-52. [PMID: 10073943]
149. McNeil AJ, Yap PL, Gore SM, Brettle RP, McColl M, Wyld R, et al. Association of HLA types A1-B8-DR3 and B27 with rapid and slow progression of HIV disease. *QJM*. 1996;89:177-85. [PMID: 8731561]
150. Goulder PJ, Phillips RE, Colbert RA, McAdam S, Ogg G, Nowak MA, et al. Late escape from an immunodominant cytotoxic T-lymphocyte response associated with progression to AIDS. *Nat Med*. 1997;3:212-7. [PMID: 9018241]
151. Goldfeld AE, Flores-Villanueva P, Vittinghoff E, Buchbinder S, Delgado JC, Leung JY, et al. HLA-B*04 homozygosity is associated with profound suppression of HIV-1 viremia and long-term non-progression to AIDS [Abstract]. In: 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, California, 30 January–2 February 2000. Alexandria, VA: Foundation for Retrovirology and Human Health; 2000. Late Breaker Abstract no. 4.
152. Hendel H, Caillat-Zucman S, Lebuane H, Carrington M, O'Brien S, Andrieu JM, et al. New class I and II HLA alleles strongly associated with opposite patterns of progression to AIDS. *J Immunol*. 1999;162:6942-6. [PMID: 10352317]
153. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853-60. [PMID: 9516219]
154. Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N Engl J Med*. 1997;337:725-33. [PMID: 9287227]
155. Perelson AS, Essunger P, Cao Y, Vesanen M, Hurley A, Saksela K, et al. Decay characteristics of HIV-1-infected compartments during combination therapy. *Nature*. 1997;387:188-91. [PMID: 9144290]
156. Ho DD. Time to hit HIV, early and hard [Editorial]. *N Engl J Med*.

- 1995;333:450-1. [PMID: 7616996]
157. **Finzi D, Hermankova M, Pierson T, Carruth LM, Buck C, Chaisson RE, et al.** Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. *Science*. 1997;278:1295-300. [PMID: 9360927]
158. **Wong JK, Hezareh M, Günthard HF, Havlir DV, Ignacio CC, Spina CA, et al.** Recovery of replication-competent HIV despite prolonged suppression of plasma viremia. *Science*. 1997;278:1291-5. [PMID: 9360926]
159. **Chun TW, Engel D, Berrey MM, Shea T, Corey L, Fauci AS.** Early establishment of a pool of latently infected, resting CD4⁽⁺⁾ T cells during primary HIV-1 infection. *Proc Natl Acad Sci U S A*. 1998;95:8869-73. [PMID: 9671771]
160. **Zhang L, Ramratnam B, Tenner-Racz K, He Y, Vesanan M, Lewin S, et al.** Quantifying residual HIV-1 replication in patients receiving combination antiretroviral therapy. *N Engl J Med*. 1999;340:1605-13. [PMID: 10341272]
161. **Finzi D, Blankson J, Siliciano JD, Margolick JB, Chadwick K, Pierson T, et al.** Latent infection of CD4⁺ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. *Nat Med*. 1999;5:512-7. [PMID: 10229227]
162. **Ramratnam B, Mittler JE, Zhang L, Boden D, Hurley A, Fang F, et al.** The decay of the latent reservoir of replication-competent HIV-1 is inversely correlated with the extent of residual viral replication during prolonged antiretroviral therapy. *Nat Med*. 2000;6:82-5. [PMID: 10613829]
163. **Furtado MR, Callaway DS, Phair JP, Kunstman K, Stanton J, Macken C, et al.** Persistence of HIV-1 transcription in peripheral-blood mononuclear cells in patients receiving potent antiretroviral therapy. *N Engl J Med*. 1999;340:1614-22. [PMID: 10341273]
164. **Martinez-Picado J, DePasquale M, Kartsonis N, Hanna G, Wong J, Finzi D, et al.** Antiretroviral resistance during successful therapy of HIV type 1 infection. *Proc Natl Acad Sci U S A*. 2000;97:10948-53. [PMID: 11005867]
165. **Saag MS, Kilby JM.** HIV-1 and HAART: a time to cure, a time to kill. *Nat Med*. 1999;5:609-11. [PMID: 10371490]
166. **Chun TW, Engel D, Mizell SB, Hallahan CW, Fischette M, Park S, et al.** Effect of interleukin-2 on the pool of latently infected, resting CD4⁺ T cells in HIV-1-infected patients receiving highly active anti-retroviral therapy. *Nat Med*. 1999;5:651-5. [PMID: 10371503]
167. **Chun TW, Davey RT Jr, Engel D, Lane HC, Fauci AS.** Re-emergence of HIV after stopping therapy. *Nature*. 1999;401:874-5. [PMID: 10553903]
168. **Stellbrink HJ, Van Lunzen J, Westby M, O'Sullivan E, Cammack N, Adam A, et al.** Influence of interleukin-2 (IL-2) on productive and latent HIV infection and on viral rebound [Abstract]. In: 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, California, 30 January–2 February 2000. Alexandria, VA: Foundation for Retrovirology and Human Health; 2000. Abstract no. 240.
169. **Ho DD.** Toward HIV eradication or remission: the tasks ahead. *Science*. 1998;280:1866-7. [PMID: 9669944]
170. **Cohen J.** Exploring how to get at—and eradicate—hidden HIV. *Science*. 1998;279:1854-5. [PMID: 9537902]
171. **Fraser C, Ferguson NM, Ghani AC, Prins JM, Lange J, Goudsmit J, et al.** Reduction of the HIV-1-infected T-cell reservoir by immune activation treatment is dose-dependent and restricted by the potency of antiretroviral drugs. *AIDS*. 2000;14:659-69. [PMID: 10807189]
172. **Prins JM, Jurriaans S, van Praag RM, Blaak H, van Rij R, Schellekens P, et al.** Immuno-activation with anti-CD3 and recombinant human IL-2 in HIV-1-infected patients on potent antiretroviral therapy. *AIDS*. 1999;13:2405-10. [PMID: 10597782]
173. **Kalams SA, Goulder PJ, Shea AK, Jones NG, Trocha AK, Ogg GS, et al.** Levels of human immunodeficiency virus type 1-specific cytotoxic T-lymphocyte effector and memory responses decline after suppression of viremia with highly active antiretroviral therapy. *J Virol*. 1999;73:6721-8. [PMID: 10400770]
174. **Ogg GS, Jin X, Bonhoeffer S, Dunbar PR, Nowak MA, Monard S, et al.** Quantitation of HIV-1-specific cytotoxic T lymphocytes and plasma load of viral RNA. *Science*. 1998;279:2103-6. [PMID: 9516110]
175. **Dalod M, Dupuis M, Deschemin JC, Sicard D, Salmon D, Delfraissy JF, et al.** Broad, intense anti-human immunodeficiency virus (HIV) ex vivo CD8⁽⁺⁾ responses in HIV type 1-infected patients: comparison with anti-Epstein-Barr virus responses and changes during antiretroviral therapy. *J Virol*. 1999;73:7108-16. [PMID: 10438796]
176. **Pitcher CJ, Quittner C, Peterson DM, Connors M, Koup RA, Maino V, et al.** HIV-1-specific CD4⁺ T cells are detectable in most individuals with active HIV-1 infection, but decline with prolonged viral suppression. *Nat Med*. 1999;5:518-25. [PMID: 10229228]
177. **Ogg GS, Jin X, Bonhoeffer S, Moss P, Nowak MA, Monard S, et al.** Decay kinetics of human immunodeficiency virus-specific effector cytotoxic T lymphocytes after combination antiretroviral therapy. *J Virol*. 1999;73:797-800. [PMID: 9847391]
178. **Musey LK, Krieger JN, Hughes JP, Schacker TW, Corey L, McElrath MJ.** Early and persistent human immunodeficiency virus type 1 (HIV-1)-specific T helper dysfunction in blood and lymph nodes following acute HIV-1 infection. *J Infect Dis*. 1999;180:278-84. [PMID: 10395840]
179. **Rosenberg ES, Walker BD.** HIV type 1-specific helper T cells: a critical host defense. *AIDS Res Hum Retroviruses*. 1998;14(Suppl 20):S143-7. [PMID: 9672231]
180. **Rosenberg ES, Billingsley JM, Caliendo AM, Boswell SL, Sax PE, Kalams SA, et al.** Vigorous HIV-1-specific CD4⁺ T cell responses associated with control of viremia. *Science*. 1997;278:1447-50. [PMID: 9367954]
181. **Binley JM, Schiller DS, Ortiz GM, Hurley A, Nixon DF, Markowitz M, et al.** The relationship between T cell proliferative responses and plasma viremia during treatment of human immunodeficiency virus type 1 infection with combination antiretroviral therapy. *J Infect Dis*. 2000;181:1249-63. [PMID: 10762561]
182. **Liszewicz J, Rosenberg E, Lieberman J, Jessen H, Lopalco L, Siliciano R, et al.** Control of HIV despite the discontinuation of antiretroviral therapy [Letter]. *N Engl J Med*. 1999;340:1683-4. [PMID: 10348681]
183. **Ortiz GM, Nixon DF, Trkola A, Binley J, Jin X, Bonhoeffer S, et al.** HIV-1-specific immune responses in subjects who temporarily contain virus replication after discontinuation of highly active antiretroviral therapy. *J Clin Invest*. 1999;104:R13-8. [PMID: 10491418]
184. **Rosenberg ES, Altfeld M, Poon SH, Phillips MN, Wilkes BM, Eldridge RL, et al.** Immune control of HIV-1 after early treatment of acute infection. *Nature*. 2000;407:523-6. [PMID: 11029005]
185. **Papasavvas E, Ortiz GM, Gross R, Sun J, Moore EC, Heymann JJ, et al.** Enhancement of human immunodeficiency virus type 1-specific CD4 and CD8 T cell responses in chronically infected persons after temporary treatment interruption. *J Infect Dis*. 2000;182:766-75. [PMID: 10950770]
186. **Ruiz L, Martinez-Picado J, Romeu J, Paredes R, Zayat M, Marfil S, et al.** Structured treatment interruption in chronically HIV-1 infected patients after long-term viral suppression. *AIDS*. 2000;14:397-403.
187. **Garcia F, Plana M, Ortiz GM, Soriano A, Vidal C, Cruceta A, et al.** Structured cyclic antiretroviral therapy interruption (STI) in chronic infection may induce immune responses against HIV-1 antigens associated with spontaneous drop in viral load [Abstract]. In: Program and Abstracts of the 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, California, 30 January–2 February 2000. Alexandria, VA: Foundation for Retrovirology and Human Health; 2000. Late Breaker Abstract no. 11.
188. **Fagard C, Lebraz M, Tortajada C, Garcia F, Bernasconi E, Battegay M, et al.** SITT: a prospective trial of strategic treatment interruptions [Abstract]. In:

- Program and Abstracts of the 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, California, 30 January–2 February 2000. Alexandria, VA: Foundation for Retrovirology and Human Health; 2000. Abstract no. 458.
189. **Lori F, Maserati R, Foli A, Seminari E, Timpone J, Lisziewicz J.** Structured treatment interruptions to control HIV-1 infection [Letter]. *Lancet*. 2000;355:287-8. [PMID: 10675080]
190. **García F, Plana M, Vidal C, Cruceta A, O'Brien WA, Pantaleo G, et al.** Dynamics of viral load rebound and immunological changes after stopping effective antiretroviral therapy. *AIDS*. 1999;13:F79-86. [PMID: 10449278]
191. **Neumann AU, Tubiana R, Calvez V, Robert C, Li TS, Agut H, et al.** HIV-1 rebound during interruption of highly active antiretroviral therapy has no deleterious effect on reinitiated treatment. Comet Study Group. *AIDS*. 1999;13:677-83. [PMID: 10397562]
192. **Lori F, Lewis M, Xu J, Varga G, Zinn D, Crabbs C, et al.** Control of HIV rebound through structured treatment interruptions during early infection. *Science*. 2000;290:1591-3. [PMID: 11090360]
193. **Deeks S, Wrin T, Liegler T, Hoh R, Hayden M, Barbour J, et al.** Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. *N Engl J Med*. 2001;344:472-80. [PMID: 11172188]
194. **Devereux HL, Youle M, Johnson MA, Loveday C.** Rapid decline in detectability of HIV-1 drug resistance mutations after stopping therapy. *AIDS*. 1999;13:F123-7. [PMID: 10630517]
195. **Miller V, Satin C, Hertogs K, Bloor S, Martinez-Picado J, D'Aquila R, et al.** Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. *AIDS*. 2000;14:2857-67. [PMID: 11153667]
196. **Dybul M, Yoder C, Belson M, Chun TW, Hallahan C, Justement JS, et al.** A randomized controlled trial of intermittent versus continuous highly active antiretroviral therapy (HAART) [Abstract]. In: Extended Version of the Abstracts: Social Science, Rights, Politics, Commitment and Action. XIII International AIDS Conference, Durban, South Africa, 9–14 July 2000. Bologna: Monduzzi Editore, International Proceedings Division; 2000. Abstract no. LbOr11.
197. **Dybul M, Yoder C, Belson M, Hallahan C, Hertogs K, Larder B, et al.** Short cycle intermittent HAART: a pilot study [Abstract]. In: Extended Version of the Abstracts: Social Science, Rights, Politics, Commitment and Action. XIII International AIDS Conference, Durban, South Africa, 9–14 July 2000. Bologna: Monduzzi Editore, International Proceedings Division; 2000. Abstract no. LbOr12.
198. **Hoff R, McNamara J.** Therapeutic vaccines for preventing AIDS: their use with HAART. *Lancet*. 1999;353:1723-4. [PMID: 10347978]
199. **Pontesilli O, Guerra EC, Ammassari A, Tomino C, Carlesimo M, Antinori A, et al.** Phase II controlled trial of post-exposure immunization with recombinant gp160 versus antiretroviral therapy in asymptomatic HIV-1-infected adults. VaxSyn Protocol Team. *AIDS*. 1998;12:473-80. [PMID: 9543445]
200. **Tsoukas CM, Raboud J, Bernard NF, Montaner JS, Gill MJ, Rachlis A, et al.** Active immunization of patients with HIV infection: a study of the effect of VaxSyn, a recombinant HIV envelope subunit vaccine, on progression of immunodeficiency. *AIDS Res Hum Retroviruses*. 1998;14:483-90. [PMID: 9566550]
201. **Ratto-Kim S, Sitz KV, Garner RP, Kim JH, Davis C, Aronson N, et al.** Repeated immunization with recombinant gp160 human immunodeficiency virus (HIV) envelope protein in early HIV-1 infection: evaluation of the T cell proliferative response. *J Infect Dis*. 1999;179:337-44. [PMID: 9878016]
202. **Trauger RJ, Daigle AE, Giermakowska W, Moss RB, Jensen F, Carlo DJ.** Safety and immunogenicity of a gp120-depleted, inactivated HIV-1 immunogen: results of a double-blind, adjuvant controlled trial. *J Acquir Immune Defic Syndr Hum Retrovirology*. 1995;10(Suppl 2):S74-82. [PMID: 7552517]
203. **Kahn JO, Cherng DW, Mayer K, Murray H, Lagakos S, et al.** Evaluation of HIV-1 immunogen, an immunologic modifier, administered to patients infected with HIV having 300 to 549 × 10⁶/L CD4 cell counts: a randomized controlled trial. *JAMA*. 2000;284:2193-202. [PMID: 11056590]
204. **Sandström E, Wahren B.** Therapeutic immunisation with recombinant gp160 in HIV-1 infection: a randomised double-blind placebo-controlled trial. Nordic VAC-04 Study Group. *Lancet*. 1999;353:1735-42. [PMID: 10347985]
205. **Churdboonchart V, Moss RB, Sirawaraporn W, Smutharaks B, Sutthent R, Jensen FC, et al.** Effect of HIV-specific immune-based therapy in subjects infected with HIV-1 subtype E in Thailand. *AIDS*. 1998;12:1521-7. [PMID: 9727574]
206. **Bratt G, Eriksson LE, Sandström E, Gilljam G, Hinkula J, Albert J, et al.** Long-term immunotherapy in HIV infection, combined with short-term antiretroviral treatment. *Int J STD AIDS*. 1999;10:514-21. [PMID: 10471100]
207. **Moss RB, Wallace RB, Giermakowska WK, Webb E, Savary J, Chamberlin-Brandt C, et al.** Phenotypic analysis of human immunodeficiency virus (HIV) type 1 cell-mediated immune responses after treatment with an HIV-1 immunogen. *J Infect Dis*. 1999;180:641-8. [PMID: 10438350]
208. **Moss RB, Giermakowska WK, Savary JR, Theofan G, Daigle AE, Richieri S, et al.** A primer on HIV type 1-specific immune function and REMUNE. *AIDS Res Hum Retroviruses*. 1998;14(Suppl 2):S167-75. [PMID: 9672235]
209. **Hel Z, Venzon D, Poudyal M, Tsai W, Giuliani L, Woodward R, et al.** Viremia control following antiretroviral treatment and therapeutic immunization during primary SIV₂₅₁ infection of macaques. *Nat Med*. 2000;6:1140-6. [PMID: 11017146]
210. **Jin X, Bauer D, Binley J, Chen D, Ramanathan M, Barsoum S, et al.** Safety and immunogenicity study on vCP1452/gp160 vaccine in patients treated with HAART for over two years [Abstract]. In: Program and Abstracts of the 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, California, 30 January–2 February 2000. Alexandria, VA: Foundation for Retrovirology and Human Health; 2000. Abstract no. 346.
211. **Jin X, Ramanathan M, Barsoum S, Bauer D, Chen D, Hurley A, et al.** Discontinuation of HAART after a course of therapeutic vaccination with ALVAC1452 and rgp160 may be associated with delayed viral rebound kinetics [Abstract]. In: Program and Abstracts of the 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, California, 30 January–2 February 2000. Alexandria, VA: Foundation for Retrovirology and Human Health; 2000. Late Breaker Abstract no. 12.
212. **Fan Z, Huang X, Borowski L, Kalinyak C, Mellors J, Rinaldo C.** Restoration of anti-HIV-1 CD8⁺ T-cell responses during potent antiretroviral drug therapy by stimulation with antigen-loaded dendritic cells [Abstract]. In: Program and Abstracts of the 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, California, 30 January–2 February 2000. Alexandria, VA: Foundation for Retrovirology and Human Health; 2000. Abstract no. 834.
213. **Wilson CC, Olson WC, Tuting T, Rinaldo CR, Lotze MT, Storkus WJ.** HIV-1-specific CTL responses primed in vitro by blood-derived dendritic cells and Th1-biasing cytokines. *J Immunol*. 1999;162:3070-8. [PMID: 10072560]
214. **Sodroski JG.** HIV-1 entry inhibitors in the side pocket. *Cell*. 1999;99:243-6. [PMID: 10555140]
215. **Chan DC, Kim PS.** HIV entry and its inhibition. *Cell*. 1998;93:681-4. [PMID: 9630213]
216. **Kilby JM, Hopkins S, Venetta TM, DiMassimo B, Cloud GA, Lee JY, et al.** Potent suppression of HIV-1 replication in humans by T-20, a peptide inhibitor of gp41-mediated virus entry. *Nat Med*. 1998;4:1302-7. [PMID: 9809555]
217. **Trkola A, Paxton WA, Monard SP, Hoxie JA, Siani MA, Thompson DA, et al.** Genetic subtype-independent inhibition of human immunodeficiency virus type 1 replication by CC and CXC chemokines. *J Virol*. 1998;72:396-404. [PMID: 9420238]
218. **Gordon CJ, Muesing MA, Proudfoot AE, Power CA, Moore JP, Trkola**

- A. Enhancement of human immunodeficiency virus type 1 infection by the CC-chemokine RANTES is independent of the mechanism of virus-cell fusion. *J Virol*. 1999;73:684-94. [PMID: 9847374]
219. Nagasawa T, Hirota S, Tachibana K, Takakura N, Nishikawa S, Kitamura Y, et al. Defects of B-cell lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBSF/SDF-1. *Nature*. 1996;382:635-8. [PMID: 8757135]
220. Endres MJ, Jaffer S, Haggarty B, Turner JD, Doranz BJ, O'Brien PJ, et al. Targeting of HIV- and SIV-infected cells by CD4-chemokine receptor pseudotypes. *Science*. 1997;278:1462-4. [PMID: 9367958]
221. Schnell MJ, Johnson JE, Buonocore L, Rose JK. Construction of a novel virus that targets HIV-1-infected cells and controls HIV-1 infection. *Cell*. 1997;90:849-57. [PMID: 9298897]
222. Mebatsion T, Finke S, Weiland F, Conzelmann KK. A CXCR4/CD4 pseudotype rhabdovirus that selectively infects HIV-1 envelope protein-expressing cells. *Cell*. 1997;90:841-7. [PMID: 9298896]
223. Cairns JS, D'Souza MP. Chemokines and HIV-1 second receptors: the therapeutic connection. *Nat Med*. 1998;4:563-8. [PMID: 9585229]
224. Cammack N. Human immunodeficiency virus type 1 entry and chemokine receptors: a new therapeutic target. *Antivir Chem Chemother*. 1999;10:53-62. [PMID: 10335399]
225. Rowland-Jones S. The role of chemokine receptors in HIV infection. *Sex Transm Infect*. 1999;75:148-51. [PMID: 10448390]
226. Proudfoot AE, Wells TN, Clapham PR. Chemokine receptors—future therapeutic targets for HIV? *Biochem Pharmacol*. 1999;57:451-63. [PMID: 9952309]
227. Roos MT, Lange JM, de Goede RE, Coutinho RA, Schellekens PT, Miedema F, et al. Viral phenotype and immune response in primary human immunodeficiency virus type 1 infection. *J Infect Dis*. 1992;165:427-32. [PMID: 1347054]
228. Lathey JL, Pratt RD, Spector SA. Appearance of autologous neutralizing antibody correlates with reduction in virus load and phenotype switch during primary infection with human immunodeficiency virus type 1 [Letter]. *J Infect Dis*. 1997;175:231-2. [PMID: 8985228]
229. Cornelissen M, Mulder-Kampinga G, Veenstra J, Zorgdrager F, Kuiken C, Hartman S, et al. Syncytium-inducing (SI) phenotype suppression at seroconversion after intramuscular inoculation of a non-syncytium-inducing/SI phenotypically mixed human immunodeficiency virus population. *J Virol*. 1995;69:1810-8. [PMID: 7853521]
230. Michael NL, Moore JP. HIV-1 entry inhibitors: evading the issue. *Nat Med*. 1999;5:740-2. [PMID: 10395316]
231. Shearer GM, Clerici M. Protective immunity against HIV infection: has nature done the experiment for us? *Immunol Today*. 1996;17:21-4. [PMID: 8652046]
232. Dolin R. Human studies in the development of human immunodeficiency virus vaccines. *J Infect Dis*. 1995;172:1175-83. [PMID: 7594651]
233. Keefer MC, Wolff M, Gorse GJ, Graham BS, Corey L, Clements-Mann ML, et al. Safety profile of phase I and II preventive HIV type 1 envelope vaccination: experience of the NIAID AIDS Vaccine Evaluation Group. *AIDS Res Hum Retroviruses*. 1997;13:1163-77. [PMID: 9310283]
234. Mascola JR, Snyder SW, Weislow OS, Belay SM, Belshe RB, Schwartz DH, et al. Immunization with envelope subunit vaccine products elicits neutralizing antibodies against laboratory-adapted but not primary isolates of human immunodeficiency virus type 1. The National Institute of Allergy and Infectious Diseases AIDS Vaccine Evaluation Group. *J Infect Dis*. 1996;173:340-8. [PMID: 8568294]
235. Zolla-Pazner S, Alving C, Belshe R, Berman P, Burda S, Chigurupati P, et al. Neutralization of a clade B primary isolate by sera from human immunodeficiency virus-uninfected recipients of candidate AIDS vaccines. *J Infect Dis*. 1997;175:764-74. [PMID: 9086128]
236. Montefiori DC, Evans TG. Toward an HIV type 1 vaccine that generates potent, broadly cross-reactive neutralizing antibodies. *AIDS Res Hum Retroviruses*. 1999;15:689-98. [PMID: 10357464]
237. Corey L, McElrath MJ, Weinhold K, Matthews T, Stablein D, Graham B, et al. Cytotoxic T cell and neutralizing antibody responses to human immunodeficiency virus type 1 envelope with a combination vaccine regimen. AIDS Vaccine Evaluation Group. *J Infect Dis*. 1998;177:301-9. [PMID: 9466515]
238. Evans TG, Keefer MC, Weinhold KJ, Wolff M, Montefiori D, Gorse GJ, et al. A canarypox vaccine expressing multiple human immunodeficiency virus type 1 genes given alone or with rgp120 elicits broad and durable CD8⁺ cytotoxic T lymphocyte responses in seronegative volunteers. *J Infect Dis*. 1999;180:290-8. [PMID: 10395842]
239. Clements-Mann ML, Weinhold K, Matthews TJ, Graham BS, Gorse GJ, Keefer MC, et al. Immune responses to human immunodeficiency virus (HIV) type 1 induced by canarypox expressing HIV-1MN gp120, HIV-1SF2 recombinant gp120, or both vaccines in seronegative adults. NIAID AIDS Vaccine Evaluation Group. *J Infect Dis*. 1998;177:1230-46. [PMID: 9593008]
240. Belshe RB, Gorse GJ, Mulligan M, Evans TG, Keefer MC, Excler JL, et al. Induction of immune responses to HIV-1 by canarypox virus (ALVAC) HIV-1 and gp120 SF-2 recombinant vaccines in uninfected volunteers. NIAID AIDS Vaccine Evaluation Group. *AIDS*. 1998;12:2407-15. [PMID: 9875578]
241. Salmon-Ceron D, Excler JL, Finkielstein L, Autran B, Gluckman JC, Sicard D, et al. Safety and immunogenicity of a live recombinant canarypox virus expressing HIV type 1 gp120 MN MN tm/gag/protease LAI (ALVAC-HIV, vCP205) followed by a p24E-V3 MN synthetic peptide (CLTB-36) administered in healthy volunteers at low risk for HIV infection. AGIS Group and L'Agence Nationale de Recherches sur Le Sida. *AIDS Res Hum Retroviruses*. 1999;15:633-45. [PMID: 10331442]
242. Ourmanov I, Bilaska M, Hirsch VM, Montefiori DC. Recombinant modified vaccinia virus ankara expressing the surface gp120 of simian immunodeficiency virus (SIV) primes for a rapid neutralizing antibody response to SIV infection in macaques. *J Virol*. 2000;74:2960-5. [PMID: 10684319]
243. Fomsgaard A. HIV-1 DNA vaccines. *Immunol Lett*. 1999;65:127-31. [PMID: 10065638]
244. Ferrari G, Humphrey W, McElrath MJ, Excler JL, Duliege AM, Clements ML, et al. Clade B-based HIV-1 vaccines elicit cross-clade cytotoxic T lymphocyte reactivities in uninfected volunteers. *Proc Natl Acad Sci U S A*. 1997;94:1396-401. [PMID: 9037064]
245. Janssens W, Buvé A, Nkengasong JN. The puzzle of HIV-1 subtypes in Africa [Editorial]. *AIDS*. 1997;11:705-12. [PMID: 9143601]
246. Falk LA, Goldenthal KL, Esparza J, Aguado MT, Osmanov S, Ballou WR, et al. Recombinant bacillus Calmette-Guérin as a potential vector for preventive HIV type 1 vaccines. *AIDS Res Hum Retroviruses*. 2000;16:91-8. [PMID: 10659047]
247. Mestecky J, Jackson S. Reassessment of the impact of mucosal immunity in infection with the human immunodeficiency virus (HIV) and design of relevant vaccines. *J Clin Immunol*. 1994;14:259-72. [PMID: 7814455]
248. Lehner T, Wang Y, Ping L, Bergmeier L, Mitchell E, Cranage M, et al. The effect of route of immunization on mucosal immunity and protection. *J Infect Dis*. 1999;179(Suppl 3):S489-92. [PMID: 10099126]
249. Lehner T, Wang Y, Cranage M, Bergmeier LA, Mitchell E, Tao L, et al. Protective mucosal immunity elicited by targeted iliac lymph node immunization with a subunit SIV envelope and core vaccine in macaques. *Nat Med*. 1996;2:767-75. [PMID: 8673922]
250. Schnell MJ, Foley H, Siler CA, McGettigan JP, Dietzschold B, Pomerantz RJ. Recombinant rabies virus as potential live-viral vaccines for HIV-1. *Proc Natl*

Acad Sci U S A. 2000;97:3544-9. [PMID: 10706640]

251. Rida W, Fast P, Hoff R, Fleming T. Intermediate-size trials for the evaluation of HIV vaccine candidates: a workshop summary. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997;16:195-203. [PMID: 9390572]

252. Francis DP, Gregory T, McElrath MJ, Belshe RB, Gorse GJ, Migasena S, et al. Advancing AIDSVAX to phase 3. Safety, immunogenicity, and plans for phase 3. *AIDS Res Hum Retroviruses*. 1998;14 Suppl 3:S325-31. [PMID: 9814961]

253. Seth A, Ourmanov I, Schmitz JE, Kuroda MJ, Lifton MA, Nickerson CE, et al. Immunization with a modified vaccinia virus expressing simian immunodeficiency virus (SIV) Gag-Pol primes for an anamnestic Gag-specific cytotoxic T-lymphocyte response and is associated with reduction of viremia after SIV challenge. *J Virol*. 2000;74:2502-9. [PMID: 10684264]

254. Egan MA, Charini WA, Kuroda MJ, Schmitz JE, Racz P, Tenner-Racz K, et al. Simian immunodeficiency virus (SIV) gag DNA-vaccinated rhesus monkeys develop secondary cytotoxic T-lymphocyte responses and control viral replication after pathogenic SIV infection. *J Virol*. 2000;74:7485-95. [PMID: 10906202]

255. Barouch D, Santra S, Schmitz J, Kuroda M, Fu T, Wagner W, et al. Control of viremia and prevention of clinical AIDS in rhesus monkeys by cytokine-augmented DNA vaccination. *Science*. 2000;290:486-92.

256. Wagner R, Shao Y, Wolf H. Correlates of protection, antigen delivery and molecular epidemiology: basics for designing an HIV vaccine. *Vaccine*. 1999;17:1706-10. [PMID: 10194826]

257. Rousseau MC, Moreau J, Delmont J. Vaccination and HIV: a review of the literature. *Vaccine*. 1999;18:825-31. [PMID: 10580195]

A wonderful fact to reflect upon, that every human creature is constituted to be that profound secret and mystery to every other. A solemn consideration, when I enter a great city by night, that every one of those darkly clustered houses encloses its own secret; that every room in every one of them encloses its own secret; that every beating heart in the hundreds of thousands of breasts there, is, in some of its imaginings, a secret to the heart nearest it! Something of the awfulness, even of Death itself, is referable to this.

Charles Dickens
A Tale of Two Cities
New York: Random House; 1996

Submitted by:
Thomas E. Finucane, MD
Johns Hopkins Bayview Medical Center
Baltimore, MD 21224

Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation (along with page number on which the quotation was found), as done for any reference.—*The Editor*