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# PATHOGENESIS AND TREATMENT OF HIV-1 INFECTION: RECENT DEVELOPMENTS

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## 1. ABSTRACT

Human immunodeficiency virus type 1 (HIV-1) is the etiologic agent of acquired immunodeficiency syndrome (AIDS) and is estimated to presently infect 24 million adults and 1.5 million children, worldwide. The pathogenesis of HIV-1-induced disease is complex and characterized by the interplay of both viral and host factors, which together determine the outcome of infection. An improved understanding of the pathogenic mechanisms of AIDS, combined with recent insights into the dynamics of viral infection, and the cellular co-receptors for HIV-1, may provide powerful new opportunities for therapeutic intervention against this virus.

## 2. INTRODUCTION

HIV-1, the causative agent of AIDS, presently infects approximately 24 million adults and 1.5 million children, worldwide (1). This brief review describes recent advances in our understanding of the pathogenesis and viral dynamics of AIDS, as well as new insights into the biology and lifecycle of HIV-1, and attempts to relate these to new and emerging approaches to the therapeutic management of HIV-1 infection.

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## 3. PATHOGENESIS OF HIV-1 INFECTION

The pathogenesis of HIV-1 infection reflects the complex interplay between virus replication, virally-induced lymphocyte killing, and the immune response of the host. The latter includes both beneficial responses, which suppress viral replication, and harmful responses which enhance replication and exacerbate cell killing. Each of these aspects of the pathogenesis of HIV-1 infection will be considered separately; HIV-1 neuropathogenesis is not discussed here but has been reviewed elsewhere (2).

### 3.1. Viral replication and viral dynamics

The typical pattern of HIV-1 infection *in vivo* is shown in Figure 1. It should be noted, however, that virus infection does not always conform to this representative scenario. For example, in about 5% of virus-positive individuals, infection is nonprogressive with no decline in $CD4^+$ lymphocyte counts and very low levels of viral RNA (3-5). This nonprogressive state may occur as the result of both host and viral factors, such as infection by naturally-occurring, attenuated, strains of HIV-1 -- such as *nef*-deleted viruses (6, 7).

In most cases, the level of HIV-1 RNA remains high during all phases of virus infection, including the period of clinical latency (8-10). Indeed, the average total HIV-1 production has been estimated at approximately 1 x $10^{10}$ virions per day (10). This reflects an active, dynamic, process in which CD4 lymphocytes are being infected and killed in large numbers. Indeed, estimated total $CD4^+$ cell

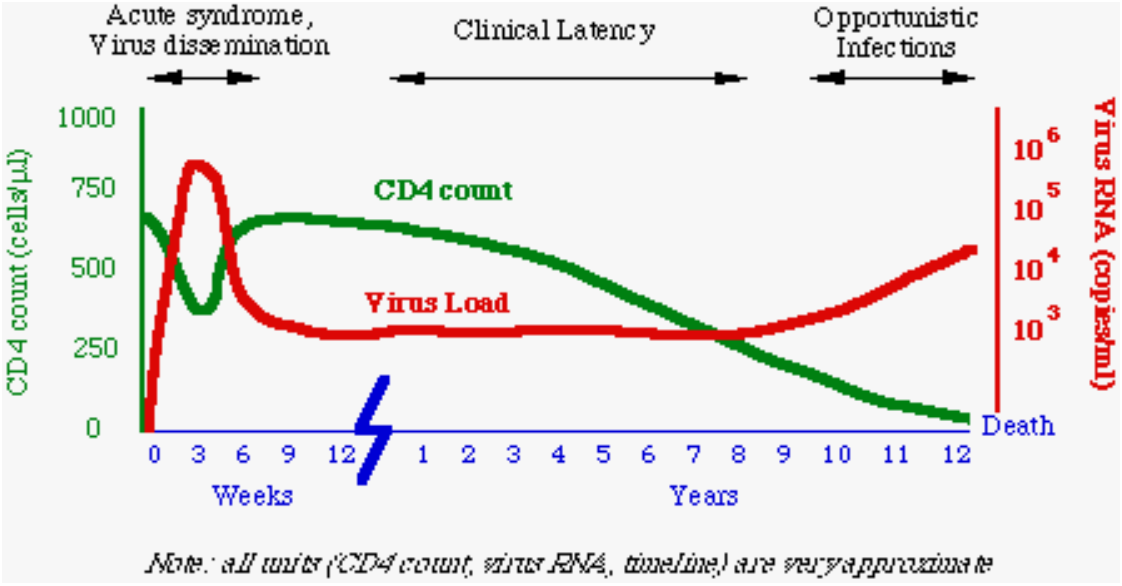


**Figure 1.** Schematic representation of the course of HIV-1 infection *in vivo*.

destruction rates are on the order of 3 x $10^9$ cells per day (8). As noted by Coffin, these findings are consistent with a simple steady-state model of HIV-1 viral dynamics, in which virus infection, cell death and cell production are in balance (11, 12). Roughly 1-2% of the body's total complement of $CD4^+$ lymphocytes (2 x $10^{11}$ cells) are eliminated, and replaced, each day over a period of many years. This level of production presumably places a high burden on the replacement system and may ultimately prove non-sustainable -- resulting in an immune collapse.

The relevance of HIV-1 dynamics to the pathogenesis of AIDS has been convincingly demonstrated by several studies. Perhaps the most compelling data are those reported by Mellors and colleagues (13). These investigators found that, among persons with equivalent baseline $CD4^+$ T cell counts, individuals with high baseline plasma HIV-1 RNA loads (>10,190 molecules/ml) died more rapidly (mean of 6.8 years) than individuals with low (< 10,190 molecules/ml) baseline plasma HIV-1 RNA loads (time to death > 10 years). A similar difference was detected in the rate of disease progression. As a result of these and other studies, plasma HIV-1 RNA determinations, which can be performed by three commercially available assays -- branched DNA (bDNA), reverse transcriptase-polymerase chain reaction (RT-PCR) and nucleic acid sequence-based amplification (NASBA) -- are likely to become increasingly important in clinical practice (14).

Interestingly, HIV-1 RNA load is relatively stable throughout much of the course of the viral infection (at least, until the onset of frank AIDS). Indeed, it appears that the steady-state, or equilibrium, level of HIV-1 RNA load is established within the first several months following virus infection. Thus, in early HIV-1 infection, a high virus burden is predictive of rapid disease progression both in adults and in children (15, 16). This suggests that the first few weeks and months following the initial HIV-1 infection may represent a key phase in the pathogenesis of AIDS, in which the virus is able to replicate to very high levels, to "seed" lymphoid organs, and to establish a state of equilibrium with its host. The "set point", at which this equilibrium occurs, may be critical to the subsequent disease progression (17). This may explain why administration of AZT during primary HIV-1 infection results in a striking improvement in the clinical outcome of infection, as measured by the rate of disease progression over time (18).

Although the level of HIV-1 RNA load in peripheral blood can be readily measured, less information has been garnered concerning viral replication in lymphoid tissues, principally due to the relative inaccessibility of these compartments. This issue has recently been addressed by Haase and colleagues, who applied a quantitative image analysis technique to analyze the viral burden in lymphoid tissues (19). A strikingly large and stable pool of extracellular virions was detected within lymphoid tissue, trapped on the surfaces of follicular dendritic cells (FDC). This FDC virus pool has been estimated to be 10 to 40 times larger than the productive virus pool, and it therefore accounts for most of the total body burden of HIV-1 RNA (roughly $10^{11}$ copies of HIV-1 RNA) (19). The FDC virus pool may be important for the perpetuation and spread of viral

infection within lymphoid tissue, and may complicate antiviral therapy, due to its relative stability.

### 3.2. Viral genetic variation

The rapid emergence of viral quasispecies (closely related but genetically distinct viral variants) is one of the hallmarks of lentiviral infections (20), both in humans and in primates. This property is also characteristic of RNA viruses as a whole, in large part due to the high mutation rate of RNA polymerases (21). In considering the genetic variation of HIV-1, it is instructive to note that the average viral generation time (defined as the interval between the release of a viral particle and the infection of a new host cell and release of a new burst of progeny virions) has been estimated at 2.6 days (10). Thus, HIV-1 replicates at a rate of 140 generations per year, for a period of ten or more years. It can be readily appreciated that this will lead to rapid and explosive genetic variation (11), since the mutation rate of HIV-1 is roughly 3 x $10^{-5}$ per base per replication cycle, and the viral genome size is $10^4$ base pairs. If $10^{10}$ new viral genomes are produced each day, then on average, every mutation at each position in the viral genome will occur several times -- in just a single day. This unprecedented genetic diversification has important implications for the evolution of viral variants with resistance to antiviral drugs. One can predict that such mutations will occur inevitably and rapidly -- except, perhaps, when multiple antiviral drugs are used in combination. This issue is discussed in more detail in section 4.

Viral genetic variation may also be driven, to some extent, by the host immune response. Recent findings by two groups of investigators, suggest that HIV-1 undergoes adaptive evolution *in vivo*, in response to selective pressure exerted by the host immune system (22, 23). As a result, viral genetic diversity is greatest in clinically healthy individuals and much less in persons with AIDS (where the immune response has become severely impaired) (22). Thus, the extent of intrahost HIV-1 evolution is to some degree related to the length of the immunocompetent period (23). It is less clear whether HIV-1 genetic diversity plays any direct role in the pathogenesis of AIDS. Nowak and colleagues have proposed the existence of an “antigenic diversity threshold”, in which the ever-expanding genetic diversity of HIV-1 eventually exhausts the capacity of the immune system to respond, resulting in an immune collapse (24). While direct support for this theory has been elusive (22, 23), it is intuitively obvious that viral variation could facilitate immune evasion. Consistent with this, Borrow *et al.* showed that primary virus infection was associated with the rapid clearance of the transmitted strain, followed by selection for a virus population comprised of strains bearing a mutation in the major immunodominant cytotoxic T-lymphocyte (CTL) epitope (25). CTL escape mutants have also been associated with the progression to AIDS, many years after the initial virus infection (26).

### 3.3. Protective host immune responses

In all likelihood, the pathogenesis of AIDS reflects a balance between viral replication and the immune response. Available evidence suggests that humoral immunity is probably not the dominant mode by which HIV-1 replication is controlled. Serum antibodies are of uncertain relevance, in part because primary HIV-1 isolates are relatively resistant to serum neutralization, unlike T-cell line-adapted strains (27-29). In addition, although HIV-1 infected long-term non-progressors produce vigorous serum antibody responses, virus strains isolated from these individuals were not neutralized by autologous sera (30). In contrast, the cellular immune response to HIV-1 may be critical in controlling viral infection and in determining the steady-state HIV-1 RNA load that is established following the primary infection (25, 31, 32). Pantaleo and colleagues have made the interesting observation that mobilization of a broad T cell receptor (TCR) repertoire during acute HIV-1 infection is associated with a relatively stable clinical course, while mobilization of a restricted subset of $CD8^+$ T cells is associated with more rapid disease progression (32). If, as these authors suggest, the $CD8^+$ T cell families which are expanded during acute infection are rapidly deleted, then it is relatively easy to understand how a broad TCR repertoire could be important in controlling the early stages of HIV-1 infection, and thereby establishing a relatively low steady-state level of HIV-1 RNA load.

Other protective aspects of the immune response may include the production of high levels of soluble inhibitors of virus infection and replication -- as first noted by Levy and colleagues (33). The most well characterized examples are the β-chemokines, macrophage inflammatory proteins (MIP) 1 alpha and β and RANTES (regulated on activation, normally T-cell expressed and secreted), which are shown in Figure 2.

The β-chemokines can interfere with the ability of M-tropic HIV-1 strains to infect T cells (34), by blocking the binding of HIV-1 gp120 to the CCR5 entry cofactor, as illustrated in Figure 3 (35-40). High levels of these chemokines have been found in exposed-uninfected persons, who are relatively resistant to HIV-1 infection (41), and these chemokines may also contribute to the control of virus replication in infected individuals. However, the β-chemokines are not effective against all HIV-1 strains or in all cell types. Indeed, these factors are effective only against infection of T cells by M-tropic strains of HIV-1. Infection of monocyte/macrophages by these same HIV-1 strains is not blocked (42, 43), and neither is the infection of T cells by T-tropic HIV-1 strains (34). The latter finding reflects the fact that T-tropic HIV-1 strains utilize a distinct entry cofactor, CXCR4 (44-46).

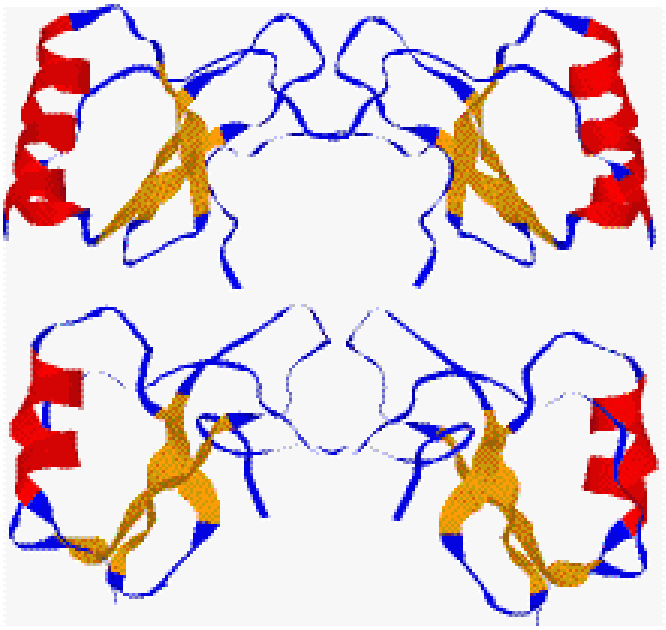

**Figure 2.** Structural representation of the β-chemokines, MIP-1β (top) and RANTES (bottom). Red coils represent a-helices and orange sheets represent β-sheets. Both chemokines are homodimers composed of identical subunits. At the amino acid level, RANTES and MIP-1β exhibit 49% identity, but structurally the two molecules are even more closely related (see above), and both bind to the same receptor, CCR5. The above molecular representations were generated with RasMol (http://www.glaxo wellcome.co.uk/netscape/software), using the PDB database files 1HRJ.PDB (RANTES) and 1HUM.PDB (MIP-1β) (http://www.pdb.bnl.gov/cgi-bin/pdbmain).

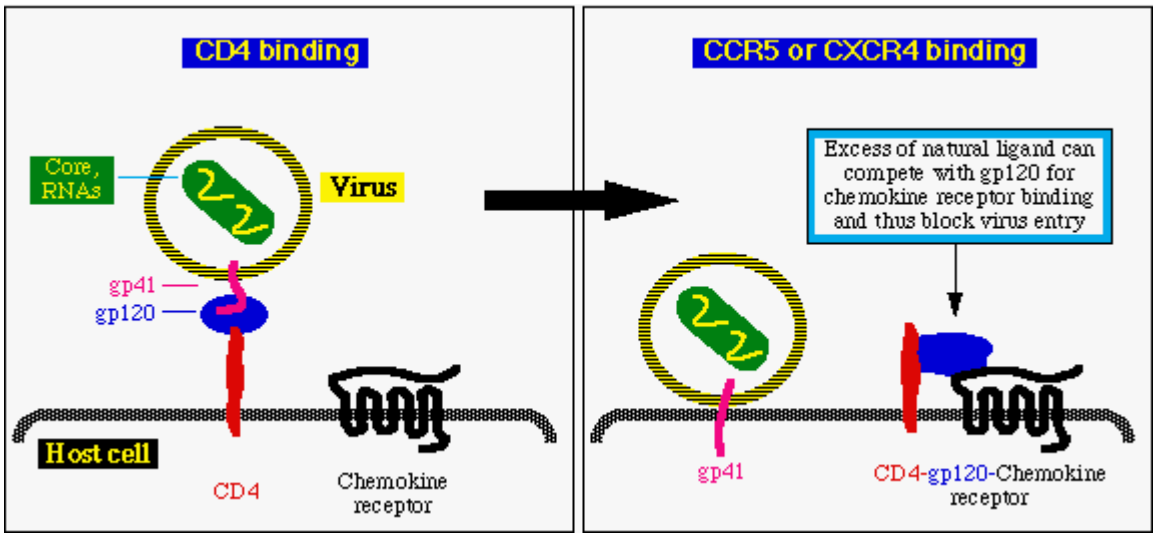


**Figure 3.** Model for HIV-1 entry in T cells. HIV-1 gp120 first binds to cellular CD4. This results in a conformational change in gp120, allowing it to bind to the chemokine receptors CCR5 or CXCR4, thereby forming a trimolecular complex (CD4-gp120-CCR/CXCR). An excess of the natural ligands for CCR5 or CXCR4 can competitively inhibit this step of infection (as noted). After binding to the chemokine receptor, gp120 is thought to become stripped off the virion, thereby exposing a hydrophobic domain at the N-terminus of gp41, which mediates fusion of the host cell and virus membranes, thereby allowing the virus core to enter the host cell cytoplasm.

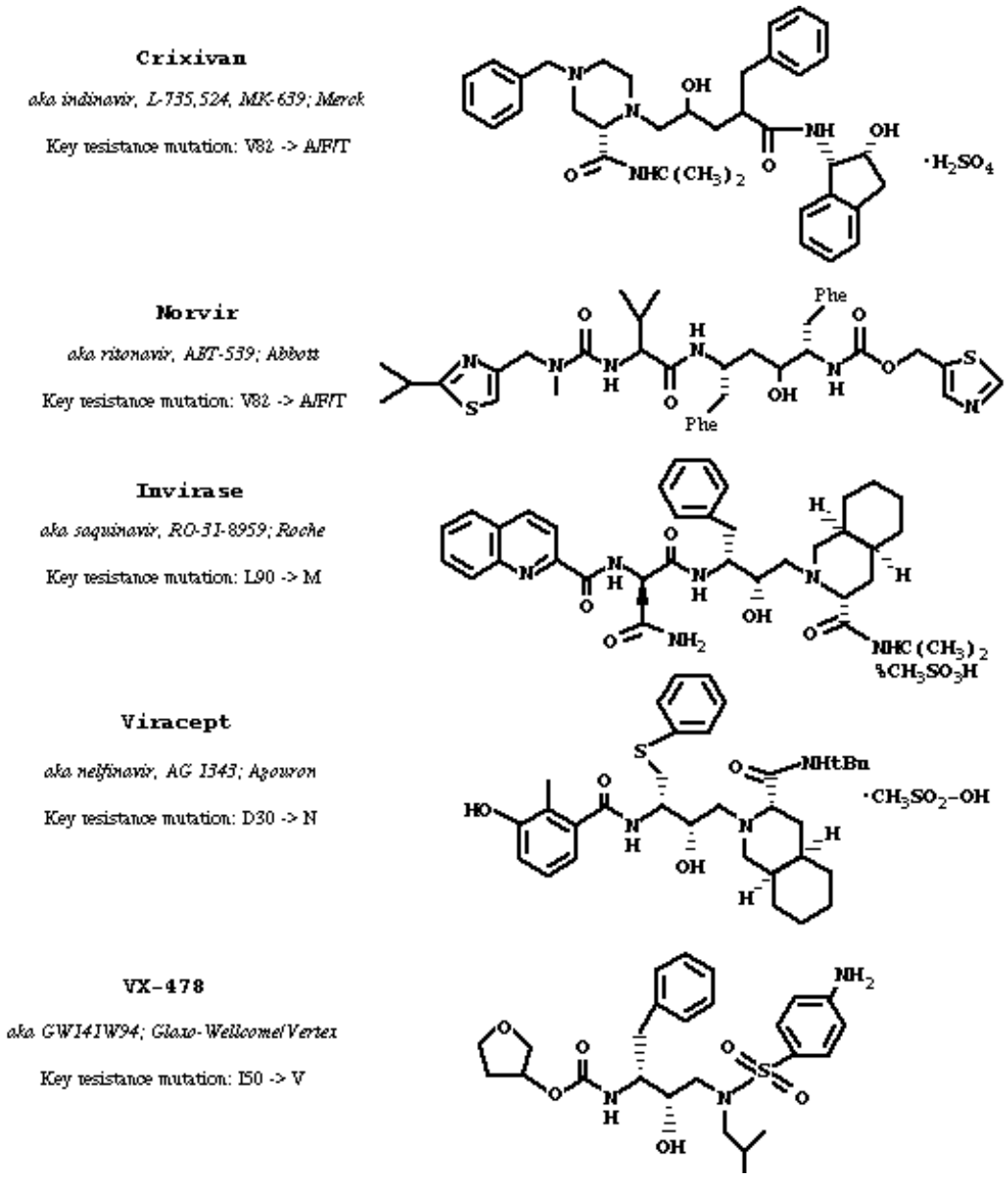


**Figure 4.** Structures of selected HIV-1 protease inhibitors. Key mutations in protease, which are critical for virus drug resistance are noted (numbers refer to the amino acid residue affected).

The failure of β-chemokines to block infection of macrophages is somewhat more surprising, since macrophages express CCR5 (43). This suggests that the process of HIV-1 entry in these cells may be different than for T cells (47, 48). This might also explain why macrophages express CXCR4 but cannot be infected by T-tropic HIV-1 strains (43).

β-chemokines are almost certainly **not** the only naturally occurring cytokines with anti-HIV-1 activity. For example, infection of T cells by T-tropic HIV-1 strains can be inhibited by the CXCR4 ligand, stromal cell-derived factor-1 (SDF-1) (45, 46). In addition, other soluble factors can inhibit HIV-1 infection, including the CD4-binding chemokine interleukin-16 (49, 50), and as-yet unidentified soluble factor(s) derived from $CD8^+$ T cells (33).

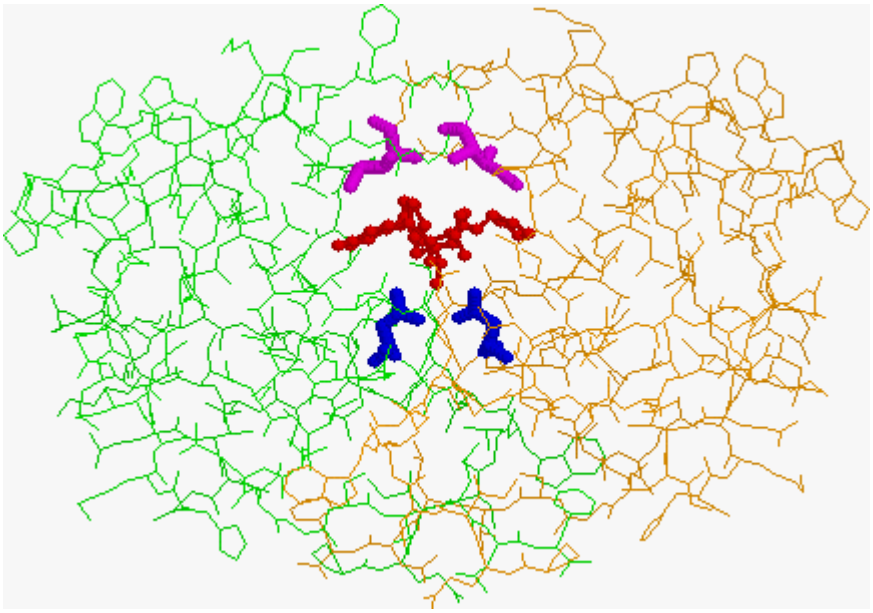

**Figure 5.** Structure of HIV-1 protease, complexed with the enzyme inhibitor VX-478. The individual protease monomers are colored orange and green. VX-478 has replaced the substrate, and is shown in red. The paired active site Asp residues (Asp25) are shown in blue, and the key residues involved in viral genetic resistance to VX-478 are shown in purple (Ile 50). This molecular representation was generated with RasMol (http://www.glaxowellcome.co.uk/netscape/software), using the PDB database file 1HPV.PDB (http://www.pdb.bnl.gov/cgi-bin/pdbmain); protease residues are shown in the "wireframe" format. A 3-D version of this figure, which can be manipulated by the reader, is available at: *http://www.bioscience.org/1992/v2/d/dewhurs1/htmls/prvxfram.html*.

### 3.4. Immunopathogenic mechanisms

Regulation of HIV-1 replication is influenced by the opposing effects of suppressive factors such as the β-chemokines and inductive factors, including endogenous proinflammatory cytokines such as tumor necrosis factor (TNF)-alpha and interleukin-6 (IL-6) (51, 52). Levels of these proinflammatory cytokines are often high during the acute phase of HIV-1 infection (53-55), particularly in individuals who experience a severe or symptomatic acute primary HIV-1 syndrome (54, 56). This may in part explain why extensive T cell activation during the early phases of HIV-1 infection is associated with more rapid disease progression (15, 56).

T cell activation may also contribute to the replication of HIV-1 during the post-acute phase of virus infection. For example, HIV-1 infection of cultured $CD4^+$ T cells is greatly enhanced in the setting of antigen-specific immune activation (57), and virus replication increases dramatically *in vivo* after vaccination of HIV-1 infected persons with a variety of immunogens (58-60). T cell activation in HIV-1 infected individuals is also associated with extensive apoptosis of virus-negative T cells (61, 62). This increased susceptibility of T cells from HIV-1 infected persons to activation-induced cell death may be important to the pathogenesis of immune deficiency and may help to explain the accelerated course of HIV-1 induced disease in areas where immune activation may be persistent or chronic due to endemic parasites and other pathogens (63).

An important corollary of the relationship between immune activation and HIV-1 replication is the prediction that immune suppression should lead to a reduction in the viral burden and perhaps even to an improvement in clinical status (64). Several studies suggest that this may be the case. For example, blockade of the endogenous proinflammatory cytokines TNF-alpha, IL-6 and interleukin-1β results in suppression of HIV-1 replication *in vitro* (52, 65). In addition, immune suppressive therapy has been associated with a rise in $CD4^+$ cell counts in asymptomatic HIV-1 infected persons (the median CD4 increase in a cohort of 44 persons who received oral prednisolone for one year was 119 cells/μl; (66)). A more aggressive immunosuppressive regimen (total lymphoid irradiation) also resulted in a transient decrease in viral burden and a lack of disease progression in simian immunodeficiency virus (SIV) infected macaques (67). These data suggest that immune

suppressive therapies may have a role in the treatment of HIV-1 infection (68).

## 4. THERAPY FOR HIV-1 INFECTION

New combination drug therapies, and the use of protease inhibitors, have fueled a new mood of optimism in the treatment of HIV-1 infection and represent one of the most exciting breakthroughs in HIV-1 research since the epidemic began. Some of the more recent developments in therapy are summarized in this section. Gene therapy for HIV-1 infection is not discussed, for reasons of space, and readers are referred to recent reviews in this area (69-72).

### 4.1. Protease inhibitors and combination therapy

Briefly, the HIV-1 Gag and Pol proteins are encoded in the form of large polypeptide precursors which must be proteolytically processed into mature proteins. The proteolytic cleavage of Gag and Pol precursor polyproteins is carried out by a virally-encoded aspartyl protease that is required for virus replication, and which has been structurally examined at the atomic level (reviewed in (73)). Using this information, enzyme inhibitors were designed (74), and their pharmocologic properties (*e.g.*, oral bioavailability) modified so as to arrive at biologically effective antiviral drugs. The first to receive Food and Drug Administration (FDA) approval, in December of 1995, was invirase (saquinavir), followed swiftly by crixivan (indinavir) and norvir (ritonavir) (see Fig. 4). Other drugs, notably viracept, are likely to follow in 1997.

HIV-1 protease is a homodimeric protein composed of two identical subunits of 99 amino acids each, and the protease inhibitors are transition state analogs which bind the enzyme much more tightly than does the natural substrate (since the substrate must be distorted to assume its transition state configuration). Thus, the presently available protease inhibitors function as competitive enzyme inhibitors. The structure of HIV-1 protease, complexed with one of its inhibitors (VX-478) is presented in Figure 5.

Protease inhibitors are typically used in combination with other antiviral drugs (reverse transcriptase inhibitors) *in vivo*, with results that can be quite impressive in many (but not all) patients. Triple drug combinations have received a widespread attention, and effective cocktails include saquinavir (invirase), zidovudine (AZT) plus zalcitabine (ddC) (75, 76) as well as norvir (indinavir), zidovudine (AZT) plus lamivudine (3TC) (77). In addition, multiple drugs which target a single viral enzyme can be combined effectively. For example, a combination of the reverse transcriptase inhibitors, nevirapine, zidovudine (AZT) and didanosine (ddI), has been shown to result in long-term immunologic and virologic improvements, relative to the treatment with zidovudine and didanosine alone (78).

Future efforts will no doubt focus on the identification of optimal drug combinations for the treatment of HIV-1 infection, and one important consideration is that of cross-resistance. Specifically, viruses with a genetic resistance to one drug may also be resistant to other, similar, compounds that target the same viral enzyme. In the case of protease inhibitors, virus strains resistant to crixivan (indinavir) are also resistant to norvir (indinavir) -- but they remain susceptible to other enzyme inhibitors (79), suggesting that dual or even triple protease inhibitor therapy might be possible. A similar situation exists with respect to the nucleoside-based inhibitors of HIV-1 reverse transcriptase, most of which do not confer cross-resistance to one another.

Given the enormous genetic diversity of HIV-1 variants present in each infected person, the emergence of HIV-1 strains with resistance to single or even multiple antiviral drugs can be expected and may even be inevitable. With this in mind, Coffin has noted that (1) therapy should be initiated early (before excessive diversity has accumulated), and (2) that the most effective antiviral drugs may be those which select for resistant strains that are genetically attenuated in some manner (11, 12). There is reason to think that this may practical. HIV-1 variants with a high-level resistance to certain protease inhibitors replicate more slowly than the wild-type viruses (80), and strains resistant to lamivudine (3TC) likewise exhibit an impaired fitness (81).

### 4.2. Future directions

Improvements in therapies for HIV-1 infection may come both from improved or novel antiviral drugs and from a better understanding of the nature of the protective and harmful host immune responses to HIV-1.

Several new classes of antiviral drugs are being developed, including inhibitors of the HIV-1 integrase (82), as well as compounds targeted against the highly conserved HIV-1 nucleocapsid protein zinc fingers involved in genome packaging and virus assembly (83). In addition, a synthetic chemokine antagonist, RANTES(9-68), has been shown to block the infection of T cells by M-tropic HIV-1 strains (84), as have the recently identified chemokine homologs encoded by human herpesvirus-8 (85). Other, virally-derived factors, might also emerge as useful anti-HIV-1 agents. For example, the putative CD4-binding protein encoded by human herpesvirus-7 can interfere with the HIV-1 infection of both T cells and macrophages (86, 87).

An alternative, or adjunctive approach to therapy may be the use of immune modulators. Prevention of deleterious responses is one possibility, and this may be

achievable through targeted blockade of specific inflammatory mediators, such as TNF-alpha. Specific inhibitors of this cytokine, notably thalidomide and pentoxifylline, are presented being investigated for their therapeutic potential -- particularly in HIV-1 infected persons with mycobacterial infections (88-90). In addition, it may be possible to facilitate or even to partially restore immune function in persons with HIV-1 infection. Examples of such approaches include the use of low-dose interleukin-2 treatment as a means of boosting $CD4^+$ T cell levels (91, 92) and *ex vivo* proliferation of $CD4^+$ cells using CD28 costimulation (93). The latter approach may also facilitate gene therapeutic approaches to HIV-1 infection, by allowing ex vivo transduction of $CD4^+$ T cells with retrovirus vectors, followed by selection and expansion of transduced cells (93).

## 5. PERSPECTIVE AND SUMMARY

Better understanding of the pathogenesis and viral dynamics of HIV-1 infection is likely to result in improvements in future antiviral therapy. Nonetheless, the past 12 to 18 months have perhaps represented the most optimistic period in AIDS research and treatment, and have led to speculation as to whether it may be possible to eradicate HIV-1 from an infected person through the long-term application of an effective antiretroviral regimen (94). These advances in HIV-1 therapy have also been paralleled by significant increases in our understanding of the basic biology of HIV-1. Most notable among these has been the identification of at least two HIV-1 entry cofactors (CCR5 and CXCR4) which are required for virus infection of T cells. Future efforts are likely to uncover additional entry cofactors, including the putative macrophage entry cofactor, and to lead to new approaches to antiviral therapy.

## 6. ACKNOWLEDGMENTS

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## 7. REFERENCES

1. T.C. Quinn: Global burden of the HIV pandemic. *Lancet* 348, 99-106 (1996)

2. S. Dewhurst, H.A. Gelbard & S.M. Fine: Neuropathogenesis of AIDS. *Mol Med Today* 2, 16-23 (1996)

3. G. Pantaleo, S. Menzo, M. Vaccarezza, C. Graziosi, O.J. Cohen, J.F. Demarest, D. Montefiori, J.M. Orenstein, C. Fox, L.K. Schrager, J.B. Margolick, S. Buchbinder, J.V. Giorgi & A.S. Fauci: Studies in subjects with long-term nonprogressive human immunodeficiency virus infection. *N Engl J Med* 332, 209-16 (1995)

4. Y. Cao, L. Qin, L. Zhang, J. Safrit & D.D. Ho: Virologic and immunologic characterization of long-term survivors of human immunodeficiency virus type 1 infection. *N Engl J Med* 332, 201-8 (1995)

5. S.P. Buchbinder, M.H. Katz, N.A. Hessol, P.M. O'Malley & S.D. Holmberg: Long-term HIV-1 infection without immunologic progression. *Aids* 8, 1123-8 (1994)

6. F. Kirchhoff, T.C. Greenough, D.B. Brettler, J.L. Sullivan & R.C. Desrosiers: Absence of intact *nef* sequences in a long-term survivor with nonprogressive HIV-1 infection. *N Engl J Med* 332, 228-32 (1995)

7. N.J. Deacon, A. Tsykin, A. Solomon, K. Smith, M. Ludford-Menting, D.J. Hooker, D.A. McPhee, A.L. Greenway, A. Ellett, C. Chatfield, V.A. Lawson, S. Crowe, A. Maerz, S. Sonza, J. Learmont, J.S. Sullivan, A. Cunningham, D. Dwyer, D. Dowton & J. Mills: Genomic structure of an attenuated quasi species of HIV-1 from a blood transfusion donor and recipients. *Science* 270, 988-91 (1995)

8. D.D. Ho, A.U. Neumann, A.S. Perelson, W. Chen, J.M. Leonard & M. Markowitz: Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature* 373, 123-6 (1995)

9. X. Wei, S.K. Ghosh, M.E. Taylor, V.A. Johnson, E.A. Emini, P. Deutsch, J.D. Lifson, S. Bonhoeffer, M.A. Nowak, B.H. Hahn, M.S. Saag & G.M. Shaw: Viral dynamics in human immunodeficiency virus type 1 infection. *Nature* 373, 117-22 (1995)

10. A.S. Perelson, A.U. Neumann, M. Markowitz, J.M. Leonard & D.D. Ho: HIV-1 dynamics *in vivo*: virion clearance rate, infected cell life-span, and viral generation time. *Science* 271, 1582-6 (1996)

11. J.M. Coffin: HIV population dynamics *in vivo*: implications for genetic variation, pathogenesis, and therapy. *Science* 267, 483-9 (1995)

12. J.M. Coffin: HIV viral dynamics. *AIDS* 10 (suppl 3), S75-S84 (1996)

13. J.W. Mellors, C.R. Rinaldo, Jr., P. Gupta, R.M. White, J.A. Todd & L.A. Kingsley: Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science* 272, 1167-70 (1996)

14. M.S. Saag, M. Holodniy, D.R. Kuritzkes, W.A. O'Brien, R. Coombs, M.E. Poscher, D.M. Jacobsen, G.M. Shaw, D.D. Richman & P.A. Volberding: HIV viral load markers in clinical practice. *Nature Med* 2, 625-9 (1996)

15. M.T. Wong, M.J. Dolan, E. Kozlow, R. Doe, G.P. Melcher, D.S. Burke, R.N. Boswell & M. Vahey: Patterns of virus burden and T cell phenotype are established early and are correlated with the rate of disease progression in human immunodeficiency virus type 1-infected persons. *J Infect Dis* 173, 877-87 (1996)

16. A. De Rossi, S. Masiero, C. Giaquinto, E. Ruga, M. Comar, M. Giacca & L. Chieco-Bianchi: Dynamics of viral replication in infants with vertically acquired human immunodeficiency virus type 1 infection. *J Clin Invest* 97, 323-30 (1996)

17. D.D. Ho: Time to hit HIV, early and hard. *N Engl J Med* 333, 450-1 (1995)

18. S. Kinloch-De Loes, B.J. Hirschel, B. Hoen, D.A. Cooper, B. Tindall, A. Carr, J.H. Saurat, N. Clumeck, A. Lazzarin, L. Mathiesen, F. Raffi, F. Antunes, J. von Overbeck, R. Luthy, M. Glauser, D. Hawkins, C. Baumberger, S. Yerly, T.V. Perneger & L. Perrin: A controlled trial of zidovudine in primary human immunodeficiency virus infection. *N Engl J Med* 333, 408-13 (1995)

19. A.T. Haase, K. Henry, M. Zupancic, G. Sedgewick, R.A. Faust, H. Melroe, W. Cavert, K. Gebhard, K. Staskus, Z.-Q. Zhang, P.J. Dailey, H.H. Balfour, A. Erice & A.S. Perelson: Quantitative image analysis of HIV-1 infection in lymphoid tissue. *Science* 274, 985-9 (1996)

20. M. Eigen: Viral quasispecies. *Scientific American* 269, 42-9 (1993)

21. J.J. Holland, J.C. De La Torre & D.A. Steinhauer: RNA virus populations as quasispecies. *Curr Top Microbiol Immunol* 176, 1-20 (1992)

22. S.M. Wolinsky, B.T. Korber, A.U. Neumann, M. Daniels, K.J. Kunstman, A.J. Whetsell, M.R. Furtado, Y. Cao, D.D. Ho, J.T. Safrit & J.A. Koup: Adaptive evolution of human immunodeficiency virus-type 1 during the natural course of infection. *Science* 272, 537-42 (1996)

23. V.V. Lukashov, C.L. Kuiken & J. Goudsmit: Intrahost human immunodeficiency virus type 1 evolution is related to length of the immunocompetent period. *J Virol* 69, 6911-6 (1995)

24. M.A. Nowak, R.M. Anderson, A.R. McLean, T.F. Wolfs, J. Goudsmit & R.M. May: Antigenic diversity thresholds and the development of AIDS. *Science* 254, 963-9 (1991)

25. P. Borrow, H. Lewicki, X. Wei, M.S. Horwitz, N. Peffer, H. Meyers, J.A. Nelson, J.E. Gairin, B.H. Hahn, M.B.A. Oldstone & G.M. Shaw: Antiviral pressure exerted by HIV-1-specific cytotoxic T lymphocytes (CTLs) during primary infection demonstrated by rapid selection of CTL escape virus. *Nature Med* 3, 205-11 (1997)

26. P.J.R. Goulder, R.E. Phillips, R.A. Colbert, S. McAdam, G. Ogg, M.A. Nowak, P. Giangrande, G. Luzzi, B. Morgan, A. Edwards, A.J. McMichael & S. Rowland-Jones: Late escape from an immunodominant cytotoxic T-lymphocyte response associated with progression to AIDS. *Nature Med* 3, 212-7 (1997)

27. N. Sullivan, Y. Sun, J. Li, W. Hofmann & J. Sodroski: Replicative function and neutralization sensitivity of envelope glycoproteins from primary and T-cell line-passaged human immunodeficiency virus type 1 isolates. *J Virol* 69, 4413-22 (1995)

28. J.P. Moore, Y. Cao, L. Qing, Q.J. Sattentau, J. Pyati, R. Koduri, J. Robinson, C.F.r. Barbas, D.R. Burton & D.D. Ho: Primary isolates of human immunodeficiency virus type 1 are relatively resistant to neutralization by monoclonal antibodies to gp120, and their neutralization is not predicted by studies with monomeric gp120. *J Virol* 69, 101-9 (1995)

29. P.J. Klasse & J.P. Moore: Quantitative model of antibody- and soluble CD4-mediated neutralization of primary isolates and T-cell line-adapted strains of human immunodeficiency virus type 1. *J Virol* 70, 3668-77 (1996)

30. D.C. Montefiori, G. Pantaleo, L.M. Fink, J.T. Zhou, J.Y. Zhou, M. Bilska, G.D. Miralles & A.S. Fauci: Neutralizing and infection-enhancing antibody responses to human immunodeficiency virus type 1 in long-term nonprogressors. *J Infect Dis* 173, 60-7 (1996)

31. D.J. Blackbourn, C.E. Mackewicz, E. Barker, T.K. Hunt, B. Herndier, A.T. Haase & J.A. Levy: Suppression of HIV replication by lymphoid tissue CD8+ cells correlates with the clinical state of HIV-infected individuals. *Proc Natl Acad Sci USA* 93, 13125-30 (1996)

32. G. Pantaleo, J.F. Demarest, T. Schacker, M. Vaccarezza, O.J. Cohen, M. Daucher, C. Graziosi, S.S. Schnittman, T.C. Quinn, G.M. Shaw, L. Perrin, G. Tambussi, A. Lazzarin, R.P. Sekaly, H. Soudeyns, L. Corey & A.S. Fauci: The qualitative nature of the primary immune response to HIV infection is a prognosticator of disease progression independent of the initial level of plasma viremia. *Proc Natl Acad Sci USA* 94, 254-8 (1997)

33. C.M. Walker, D.J. Moody, D.P. Stites & J.A. Levy: CD8+ lymphocytes can control HIV infection *in vitro* by suppressing virus replication. *Science* 234, 1563-6 (1986)

34. F. Cocchi, A.L. DeVico, A. Garzino-Demo, S.K. Arya, R.C. Gallo & P. Lusso: Identification of RANTES, MIP-1 alpha, and MIP-1 beta as the major HIV-suppressive factors produced by CD8+ T cells. *Science* 270, 1811-5 (1995)

35. G. Alkhatib, C. Combadiere, C.C. Broder, Y. Feng, P.E. Kennedy, P.M. Murphy & E.A. Berger: CC CKR5: a RANTES, MIP-1alpha, MIP-1beta receptor as a fusion cofactor for macrophage-tropic HIV-1. *Science* 272, 1955-8 (1996)

36. T. Dragic, V. Litwin, G.P. Allaway, S.R. Martin, Y. Huang, K.A. Nagashima, C. Cayanan, P.J. Maddon, R.A. Koup, J.P. Moore & W.A. Paxton: HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. *Nature* 381, 667-73 (1996)

37. H. Deng, R. Liu, W. Ellmeier, S. Choe, D. Unutmaz, M. Burkhart, P. Di Marzio, S. Marmon, R.E. Sutton, C.M. Hill, C.B. Davis, S.C. Peiper, T.J. Schall, D.R. Littman & N.R. Landau: Identification of a major co-receptor for primary isolates of HIV-1. *Nature* 381, 661-6 (1996)

38. H. Choe, M. Farzan, Y. Sun, N. Sullivan, B. Rollins, P.D. Ponath, L. Wu, C.R. Mackay, G. LaRosa, W. Newman, N. Gerard, C. Gerard & J. Sodroski: The beta-chemokine receptors CCR3 and CCR5 facilitate infection by primary HIV-1 isolates. *Cell* 85, 1135-48 (1996)

39. L. Wu, N.P. Gerard, R. Wyatt, H. Choe, C. Parolin, N. Ruffing, A. Borsetti, A.A. Cardoso, E. Desjardin, W. Newman, C. Gerard & J. Sodroski: CD4-induced interaction of primary HIV-1 gp120 glycoproteins with the chemokine receptor CCR-5. *Nature* 384, 179-83 (1996)

40. A. Trkola, T. Dragic, J. Arthos, J.M. Binley, W.C. Olson, G.P. Allaway, C. Cheng-Mayer, J. Robinson, P.J. Maddon & J.P. Moore: CD4-dependent, antibody-sensitive interactions between HIV-1 and its co-receptor CCR-5. *Nature* 384, 184-7 (1996)

41. W.A. Paxton, S.R. Martin, D. Tse, T.R. O'Brien, J. Skurnick, N.L. VanDevanter, N. Padian, J.F. Braun, D.P. Kotler, S.M. Wolinsky & R.A. Koup: Relative resistance to HIV-1 infection of CD4 lymphocytes from persons who remain uninfected despite multiple high-risk sexual exposure. *Nature Med* 2, 412-7 (1996)

42. H. Schmidtmayerova, B. Sherry & M. Bukrinsky: Chemokines and HIV replication. *Nature* 382, 767 (1996)

43. H. Moriuchi, M. Moriuchi, C. Combadiere, P.M. Murphy & A.S. Fauci: CD8+ T-cell-derived soluble factor(s), but not beta-chemokines RANTES, MIP-1alpha, and MIP-1beta, suppress HIV-1 replication in monocyte/macrophages. *Proc Natl Acad Sci USA* 93, 15341-5 (1996)

44. Y. Feng, C.C. Broder, P.E. Kennedy & E.A. Berger: HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. *Science* 272, 872-7 (1996)

45. E. Oberlin, A. Amara, F. Bacherlie, F. Arenzana-Seisdedos, O. Schwartz, J.-M. Heard, I. Clark-Lewis, D.F. Legler, M. Loetscher, M. Baggiolini & B. Moser: The CXC chemokine SDF-1 is the ligand for LESTR/fusin and prevents infection by T-cell-line-adapted HIV-1. *Nature* 382, 833-7 (1996)

46. C.C. Bleul, M. Farzan, H. Choe, C. Parolin, I. Clark-Lewis, J. Sodroski & T.A. Springer: The lymphocyte chemoattractant SDF-1 is a ligand for LESTR/fusin and blocks HIV-1 entry. *Nature* 382, 829-33 (1996)

47. C. Cheng-Mayer, R. Liu, N.R. Landau & L. Stamatatos: Macrophage tropism of human immunodeficiency virus type 1 and utilization of the CC-CKR-5 coreceptor. *J Virol* 71, 1657-61 (1997)

48. M.T. Dittmar, A. McKnight, G. Simmons, P.R. Clapham, R.A. Weiss & P. Simmonds: HIV-1 tropism and co-receptor use. *Nature* 385, 495-6 (1997)

49. M. Baier, A. Werner, N. Bannert, K. Metzner & R. Kurth: HIV suppression by interleukin-16. *Nature* 378, 563 (1995)

50. J.W. Maciaszek, N.A. Parada, W.W. Cruikshank, D.M. Center, H. Kornfeld & G.A. Viglianti: IL-16 represses HIV-1 promoter activity. *J Immunol* 158, 5-8 (1997)

51. A.S. Fauci: Host factors and the pathogenesis of HIV-induced disease. *Nature* 384, 529-34 (1996)

52. A.L. Kinter, M. Ostrowski, D. Goletti, A. Oliva, D. Weissman, K. Gantt, E. Hardy, R. Jackson, L. Ehler & A.S. Fauci: 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 USA* (1996)

53. W. Barcellini, G.P. Rizzardi, G. Poli, G. Tambussi, C. Velati, P.L. Meroni, A.G. Dalgleish & A. Lazzarin: Cytokines and soluble receptor changes in the transition from primary to early chronic HIV type 1 infection. *AIDS Research and Human Retroviruses* 12, 325-34 (1996)

54. G.P. Rizzardi, W. Barcellini, G. Tambussi, F. Lillo, M. Malnati, L. Perrin & A. Lazzarin: Plasma levels of

soluble CD30, tumor necrosis factor (TNF)-alpha and TNF receptors during primary HIV-1 infection: correlation with HIV-1 RNA and the clinical outcome. *AIDS* 10, F45-F50 (1996)

55. C. Graziosi, K.R. Gantt, M. Vaccarezza, J.F. Demarest, M. Daucher, M.S. Saag, G.M. Shaw, T.C. Quinn, O.J. Cohen, C.C. Welbon, G. Pantaleo & A.S. Fauci: Kinetics of cytokine expression during primary human immunodeficiency virus type 1 infection. *Proc Natl Acad Sci USA* 93, 4386-91 (1996)

56. A. Cossarizza, C. Ortolani, C. Mussini, V. Borghi, G. Guaraldi, N. Mongiardo, E. Bellesia, M.G. Franceschini, B. De Rienzo & C. Franceschi: Massive activation of immune cells with an intact T cell repertoire in acute human immunodeficiency virus syndrome. *J Infect Dis* 172, 105-12 (1995)

57. D. Weissman, T.D. Barker & A.S. Fauci: The efficiency of acute infection of CD4+ T cells is markedly enhanced in the setting of antigen-specific immune activation. *J Exp Med* 183, 687-92 (1996)

58. S. Stanley, M.A. Ostrowski, J.S. Justement, K. Gantt, S. Hedayati, M. Mannix, K. Roche, D.J. Schwartzentruber, C.H. Fox & A.S. Fauci: Effect of immunization with a common recall antigen on viral expression in patients infected with human immunodeficiency virus type 1. *N Engl J Med* 334, 1222-30 (1996)

59. S.I. Staprans, B.L. Hamilton, S.E. Follansbee, T. Elbeik, P. Barbosa, R.M. Grant & M.B. Feinberg: Activation of virus replication after vaccination of HIV-1-infected individuals. *J Exp Med* 182, 1727-37 (1995)

60. B. Brichacek, S. Swindells, E.N. Janoff, S. Pirruccello & M. Stevenson: Increased plasma human immunodeficiency virus type 1 burden following antigenic challenge with pneumococcal vaccine. *J Infect Dis* 174, 1191-9 (1996)

61. M.L. Gougeon, H. Lecoeur, A. Dulioust, M.G. Enouf, M. Crouvoiser, C. Goujard, T. Debord & L. Montagnier: Programmed cell death in peripheral lymphocytes from HIV-infected persons: increased susceptibility to apoptosis of CD4 and CD8 T cells correlates with lymphocyte activation and with disease progression. *J Immunol* 156, 3509-20 (1996)

62. C.A. Muro-Cacho, G. Pantaleo & A S. Fauci: Analysis of apoptosis in lymph nodes of HIV-infected persons. Intensity of apoptosis correlates with the general state of activation of the lymphoid tissue and not with stage of disease or viral burden. *J Immunol* 154, 5555-66 (1995)

63. T.C. Quinn, P. Piot, J.B. McCormick, F.M. Feinsod, H. Taelman, B. Kapita, W. Stevens & A.S. Fauci: Serologic and immunologic studies in patients with *AIDS* in North America and Africa. The potential role of infectious agents as cofactors in human immunodeficiency virus infection. *JAMA* 257, 2617-21 (1987)

64. A.G. Dalgleish: The immune response to HIV: potential for immunotherapy? *Immunol Today* 16, 356-8 (1995)

65. A.L. Kinter, G. Poli, L. Fox, E. Hardy & A.S. Fauci: HIV replication in IL-2-stimulated peripheral blood mononuclear cells is driven in an autocrine/paracrine manner by endogenous cytokines. *J Immunol* 154, 2448-59 (1995)

66. J.M. Andrieu, W. Lu & R. Levy: Sustained increases in CD4 cell counts in asymptomatic human immunodeficiency virus type 1-seropositive patients treated with prednisolone for 1 year. *J Infect Dis* 171, 523-30 (1995)

67. P.N. Fultz, R.S. Schwiebert, L. Su & M.M. Salter: Effects of total lymphoid irradiation on SIV-infected macaques. *AIDS Res Hum Retrovir* 11, 1517-27 (1995)

68. W.C. Greene: Denying HIV safe haven. *N Engl J Med* 334, 1264-5 (1996)

69. D.B. Kohn & N. Sarver: Gene therapy for HIV-1 infection. *Advances in Experimental Medicine & Biology* 394, 421-8 (1996)

70. M. Caruso: Gene therapy against cancer and HIV infection using the gene encoding herpes simplex virus thymidine kinase. *Mol Med Today* 2, 212-7 (1996)

71. E.M. Poeschla & F. Wong-Staal: Gene therapy and HIV disease. *AIDS Clin Rev* 1, 1-45 (1995)

72. S.H. Bridges & N. Sarver: Gene therapy and immune restoration for HIV disease. *Lancet* 345, 427-32 (1995)

73. C. Ezzell: Emergence of the protease inhibitors: a better class of AIDS drugs? *J NIH Res* 8, 41-5 (Jan. 1996)

74. P.Y. Lam, P.K. Jadhav, C.J. Eyermann, C.N. Hodge, Y. Ru, L.T. Bacheler, J.L. Meek, M.J. Otto, M.M. Rayner, Y.N. Wong, C.H. Chang, P.C. Weber, D.A. Jackson, T.R. Sharpe & S. Erickson-Viitanen: Rational design of potent, bioavailable, nonpeptide cyclic ureas as HIV protease inhibitors. *Science* 263, 380-4 (1994)

75. A.C. Collier, R.W. Coombs, D.A. Schoenfeld, R. Bassett, A. Baruch & L. Corey: Combination therapy with

zidovudine, didanosine and saquinavir. *Antiviral Res* 29, 99 (1996)

76. A.C. Collier, R.W. Coombs, D.A. Schoenfeld, R.L. Bassett, J. Timpone, A. Baruch, M. Jones, K. Facey, C. Whitacre, V.J. McAuliffe, H.M. Friedman, T.C. Merigan, R.C. Reichman, C. Hooper & L. Corey: Treatment of human immunodeficiency virus infection with saquinavir, zidovudine, and zalcitabine. AIDS Clinical Trials Group. *N Engl J Med* 334, 1011-7 (1996)

77. R. Gulick, J. Mellors, D. Havlir, J. Eron, C. Gonzalezi, D. McMahon, D. Richman, F. Valentine, L. Jonas, A. Meibohm, R. Chiou, P. Deutsch, E. Emini & J. Chodakewitz: Potent and sustained antiretroviral activity of indinavir (IDV) in combination with zidovudine (ZDV) and lamivudine (3TC). *Abstract LB7, 3rd Conference on Retroviruses and Opportunistic Infections, Washington, DC* (Jan. 28 - Feb. 1,1996)

78. R.T. D'Aquila, M.D. Hughes, V.A. Johnson, M.A. Fischl, J.P. Sommadossi, S.H. Liou, J. Timpone, M. Myers, N. Basgoz, M. Niu & M.S. Hirsch: Nevirapine, zidovudine, and didanosine compared with zidovudine and didanosine in patients with HIV-1 infection. A randomized, double-blind, placebo-controlled trial. National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group Protocol 241 Investigators. *Ann Intern Med* 124, 1019-30 (1996)

79. A. Molla, M. Korneyeva, Q. Gao, S. Vasavanonda, P.J. Schipper, H.M. Mo, M. Markowitz, T. Chernyavskiy, P. Niu, N. Lyons, A. Hsu, G.R. Granneman, D.D. Ho, C.A. Boucher, J.M. Leonard, D.W. Norbeck & D.J. Kempf: Ordered accumulation of mutations in HIV protease confers resistance to ritonavir. *Nature Med* 2, 760-6 (1996)

80. G. Croteau, L. Doyon, D. Thibeault, G. McKercher, L. Pilote & D. Lamarre: Impaired fitness of human immunodeficiency virus type 1 variants with high-level resistance to protease inhibitors. *J Virol* 71, 1089-96 (1997)

81. N.K. Back, M. Nijhuis, W. Keulen, C.A. Boucher, B.O. Oude Essink, A.B. van Kuilenburg, A.H. van Gennip & B. Berkhout: Reduced replication of 3TC-resistant HIV-1 variants in primary cells due to a processivity defect of the reverse transcriptase enzyme. *EMBO J* 15, 4040-9 (1996)

82. W.E. Robinson, Jr., M.G. Reinecke, S. Abdel-Malek, Q. Jia & S.A. Chow: Inhibitors of HIV-1 replication that inhibit HIV integrase. *Proc Natl Acad Sci USA* 93, 6326-31 (1996)

83. W.G. Rice, J.G. Supko, L. Malspeis, R.W. Buckheit, Jr., D. Clanton, M. Bu, L. Graham, C.A. Schaeffer, J.A. Turpin, J. Domagala, R. Gogliotti, J.P. Bader, S.M. Halliday, L. Coren, R.C. Sowder II, L.O. Arthur & L.E. Henderson: Inhibitors of HIV nucleocapsid protein zinc fingers as candidates for the treatment of AIDS. *Science* 270, 1194-7 (1995)

84. F. Arenzana-Seisdedos, J.-L. Virelizier, D. Rousset, I. Clark-Lewis, P. Loetscher, B. Moser & M. Baggiolini: HIV blocked by a chemokine antagonist. *Nature* 383, 400 (1996)

85. P.S. Moore, C. Boshoff, R.A. Weiss & Y. Chang: Molecular mimicry of human cytokine and cytokine response pathway genes by KSHV. *Science* 274, 1739-44 (1996)

86. P. Lusso, P. Secchiero, R.W. Crowley, A. Garzino-Demo, Z.N. Berneman & R.C. Gallo: CD4 is a critical component of the receptor for human herpesvirus 7: interference with human immunodeficiency virus. *Proc Natl Acad Sci USA* 91, 3872-6 (1994)

87. R.W. Crowley, P. Secchiero, D. Zella, A. Cara, R.C. Gallo & O. Lusso: Interference between human herpesvirus 7 and HIV-1 in mononuclear phagocytes. *J Immunol* 156, 2004-8 (1996)

88. R.S. Wallis, P. Nsubuga, C. Whalen, R.D. Mugerwa, A. Okwera, D. Oette, J.B. Jackson, J.L. Johnson & J.J. Ellner: Pentoxifylline therapy in human immunodeficiency virus-seropositive persons with tuberculosis: a randomized, controlled trial. *J Infect Dis* 174, 727-33 (1996)

89. B.J. Dezube & M.M. Lederman: Pentoxifylline for the treatment of HIV infection and its complications. *Journal of Cardiovascular Pharmacology* 25, S139-42 (1995)

90. J.D. Klausner, S. Makonkawkeyoon, P. Akarasewi, K. Nakata, W. Kasinrerk, L. Corral, R.L. Dewar, H.C. Lane, V.H. Freedman & G. Kaplan: The effect of thalidomide on the pathogenesis of human immunodeficiency virus type 1 and M. tuberculosis infection. *J.A.I.D.S.* 11, 247-57 (1996)

91. E.L. Jacobson, F. Pilaro & K.A. Smith: Rational interleukin 2 therapy for HIV positive individuals: daily low doses enhance immune function without toxicity. *Proc Natl Acad Sci USA* 93, 10405-10 (1996)

92. J.A. Kovacs, S. Vogel, J.M. Albert, J. Falloon, R.T. Davey, Jr., R.E. Walker, M.A. Polis, K. Spooner, J.A. Metcalf, M. Baseler, G. Fyfe & H.C. Lane: Controlled trial of interleukin-2 infusions in patients infected with

the human immunodeficiency virus. *N Engl J Med* 335, 1350-6 (1996)

93. B.L. Levine, J.D. Mosca, J.L. Riley, R.G. Carroll, M.T. Vahey, L.L. Jagodzinski, K.F. Wagner, D.L. Mayers, D.S. Burke, O.S. Weislow, D.C. St. Louis & C.H. June: Antiviral effect and ex vivo CD4+ T cell proliferation in HIV-positive patients as a result of CD28 costimulation. *Science* 272, 1939-43 (1996)

94. E. Pennisi & J. Cohen: Eradicating HIV from a patient: not just a dream? *Science* 272, 1884 (1996)