Perspectives

Insights in HIV Pathogenesis and Antiviral Control 4
H. Clifford Lane, M.D.

Effects of HIV and Antiretroviral Treatment on CD4+ T Cells • Evaluation of Host Immune Response

HIV Vaccine Research: Problems and Progress 9
Richard A. Koup, M.D.

Objectives in Vaccine Development • Is Vaccine-Induced Immunity Against HIV Possible? • Inducing Neutralizing Antibody Response • CTL-Based Vaccines • Status of Vaccine Development

Current Status of New Antiretroviral Drugs in Development 14
Roy M. Gulick, M.D., M.P.H.

HIV Nucleoside Reverse Transcriptase Inhibitors • HIV Nonnucleoside Reverse Transcriptase Inhibitors • HIV Protease Inhibitors • HIV Entry Inhibitors • HIV Integrase Inhibitors

Reprint

Antiretroviral Treatment for Adult HIV Infection Insert in 2002: Updated Recommendations of the International AIDS Society-USA Panel
JAMA. 2002;288:222-235.
About This Issue

This issue contains 3 Perspectives articles based on the International AIDS Society–USA continuing medical education courses held in Atlanta, Chicago, and Washington, DC, in March, April, and May 2002. H. Clifford Lane, MD, discussed aspects of the interaction between HIV and the host immune response and the development of immune-based therapies and vaccines. Richard A. Koup, MD, reviewed ongoing efforts to develop preventative HIV vaccines. Among the approaches discussed were vaccines that induce neutralizing antibodies to HIV and those employing cytolytic T lymphocytes. At the course in Washington, DC, Roy M. Gulick, MD, MPH, discussed characteristics of select antiretroviral drugs in development, including new reverse transcriptase and protease inhibitors, as well as drugs that act on new targets: HIV entry and integration.

Also included in this issue is a reprint of the recently published treatment recommendations for antiretroviral therapy in adult HIV infection by the International AIDS Society–USA Panel. The panel, currently composed of 17 international HIV experts, was initially convened in 1996. Its 2002 recommendations discuss when to start antiretroviral therapy, which initial regimens to use, when to change therapy in response to treatment failure, and which regimens to use in the setting of treatment failure.

The November/December issue will include additional reviews of clinical topics in HIV medicine as well as a new update of drug resistance mutations in HIV-1 from the International AIDS Society–USA Drug Resistance Mutations Group.

Topics in HIV Medicine™

Topics in HIV Medicine (formerly Improving the Management of HIV Disease) is published by the International AIDS Society–USA. This publication is intended to be a resource for physicians and other health care practitioners who are actively involved in HIV and AIDS care.

Editorial Policy

The views and opinions expressed in this publication are those of the contributors and do not necessarily reflect the views or recommendations of the International AIDS Society–USA. Topics in HIV Medicine is supported through unrestricted educational grants from several commercial companies that are committed to supporting CME in the field of HIV and AIDS. In the interest of an objective, balanced, and scientifically rigorous publication, the International AIDS Society–USA seeks funding from companies with competing products, these companies have no input or control over the publication content or the selection of contributors.

All authors and contributors provide disclosures of financial interests, and this information is available at the end of each article. This publication may contain information about the investigational uses of drugs or products that are not approved by the US Food and Drug Administration. Please consult full prescribing information before using any medication or product mentioned in Topics in HIV Medicine.

Copyrights

The contents of Topics in HIV Medicine are protected by copyright. We welcome reference to and use of portions of this publication; however, we request that permission to reproduce or use any part of this publication be obtained from the International AIDS Society–USA. In the case of reprinted or adapted materials where the International AIDS Society–USA does not own the copyright, permission to reproduce these materials must be obtained directly from the original source.

Subscription Information

Topics in HIV Medicine is published 4 to 6 times a year. To obtain a complimentary subscription or notify the International AIDS Society–USA of a change in address, please contact the International AIDS Society–USA at the address listed below or use the Subscription Request/Address Change form at the back of this issue.

Correspondence

Topics in HIV Medicine welcomes editorial correspondence. Address letters to:

Editor, Topics in HIV Medicine
International AIDS Society–USA
1001 B O’Reilly Avenue
San Francisco, CA 94129-1125
Phone: (415) 561-6720
Fax: (415) 561-6740
Web site: http://www.iasusa.org
E-mail: topics@iasusa.org

On the Web

Current and previous issues of Topics in HIV Medicine are available online at www.iasusa.org.

Printed in USA • August 2002
© 2002 International AIDS Society–USA
Insights in HIV Pathogenesis and Antiviral Control 4
H. Clifford Lane, M.D.

HIV Vaccine Research: Problems and Progress 9
Richard A. Koup, M.D.

Current Status of New Antiretroviral Drugs in Development 14
Roy M. Gulick, M.D., M.P.H.

JAMA. 2002;288:222-235.

World Health Organization Guidelines for Scaling Up Antiretroviral Therapy in Resource-Limited Settings 8

Clinical Pathway Webcast: Lectures From the Ryan White CARE Act 2002 All Grantee Conference 20

Guidelines for Authors and Contributors 21

Subscription Request 22

Educational Programs of the International AIDS Society–USA 23
Perspective

Insights in HIV Pathogenesis and Antiviral Control

At the March 2002 International AIDS Society–USA course in Atlanta, H. Clifford Lane, MD, discussed aspects of the interaction between HIV and the host immune response. Greater understanding of this complex interaction has aided development of immune-based therapies and vaccines.

The immune systems of individuals with HIV infection are characterized by an immunodeficiency reflected in the loss of CD4+ T cells, coupled with immune system activation reflected in an increased T-cell turnover and functional immunosuppression. In general, the state of the immune system comprises the dynamic interactions of the activity of HIV, the HIV-specific immune response, and the regenerative activity of the immune system.

Effects of HIV and Antiretroviral Treatment on CD4+ T Cells

Characteristics of the immunodeficiency observed in HIV infection include a decline in total CD4+ T-cell number, a preferential loss of CD4+ T cells with a “naive” phenotype, and a skewing of the T-cell receptor repertoire. To understand the effects of infection on CD4+ T-cell dynamics and characteristics, it is important to know how the CD4+ T-cell pool is generated and maintained under normal conditions. Undifferentiated stem cells undergo transit through the thymus, where T-cell receptor genes in germ-line configuration are rearranged to form functional genes encoding the T-cell receptor proteins. After undergoing positive and negative selection, the cells exit the thymus capable of recognizing self and antigen, with each cell having a defined antigen specificity (conferring by expression of an immune globulin-gene-like rearranged heterodimeric receptor). The CD4+ T cells, which act to stimulate and coordinate the activity of immune effector cells, proliferate in response to processed antigen presented in association with class II major histocompatibility complex alloantigens and mitogens. The cells are considered “naive” until they encounter their specified antigens, at which point they become “memory” cells. Naive cells are characterized by surface expression of the high-molecular-weight CD45R isoform CD45RA, and memory cells are characterized by expression of the low-molecular-weight isoform CD45RO. At birth, virtually all CD4+ cells are in the naive cell pool; during subsequent increasing exposure to antigen, clonal expansion of the memory cells and constriction of the CD4+ T-cell pool results in an increasing proportion of memory cells in the total pool.

Studies in patients with HIV infection indicate that progressive reduction of the total CD4+ cell count is associated with a disproportionate reduction in the naive cell compartment (Connors et al, Nat Med, 1997). Under potent antiretroviral therapy, HIV-infected patients with significant numbers of both naive and memory cells exhibit immediate increases in both compartments. If there has been severe depletion of the CD4+ T-cell pool, increases are seen predominantly in the memory compartment. Such data suggest that the increase in total CD4+ cell count observed with potent therapy reflects peripheral expansion of the cells present prior to therapy.

To study characteristics of T-cell production and death, a number of investigators have used DNA-labeling techniques such as bromodeoxyuridine (BrdU) labeling. In this technique, subjects undergo a 30-minute infusion of BrdU, which is incorporated into the cellular genomic DNA, and blood or lymph tissue is then periodically sampled. Samples are stained for cell surface markers and BrdU labeling; by use of flow cytometry, the numbers of cells produced during the BrdU pulse and their decay rate following the pulse can be determined. In one study using this technique, investigators examined the ratio of lymph node to blood of labeled CD4+ and CD8+ T cells and B cells at 4 hours, 1 day, and 3 days after BrdU infusion. Their results indicate that for the population of labeled T cells, cell division immediately after labeling occurs preferentially in the lymph node. After 1 day, however, labeled cells are equally distributed between the lymph node and

Dr Lane is Clinical Director of the National Institute of Allergy and Infectious Diseases in Bethesda, Md.

Figure 1. Comparison of change in CD4+ T-cell production in 1 patient indicated by bromodeoxyuridine (BrdU) labeling in blood samples before and 12 weeks after initiation of potent antiretroviral therapy. Inset shows difference in lymph node sample at 6 hours after BrdU pulse. Adapted with permission from Kovacs et al, J Exp Med, 2001.
the blood. These findings suggest that monitoring of T-cell characteristics in the peripheral blood provides a good reflection of characteristics in the lymphoid tissues. Extended monitoring of the labeled cells shows that the T-cell pool consists of cells with a rapid turnover rate, as well as cells with a slow decay rate.

This technique was used to assess CD4+ T-cell production before and after initiation of potent antiretroviral therapy in a group of HIV-infected patients (Figure 1). BrdU labeling before initiation of treatment and at 12 weeks after initiation of treatment showed that CD4+ cell production as measured in the peripheral blood was decreased by approximately 75% during antiretroviral therapy, with results being similar in blood and lymph node tissue. These data strongly suggest that there is no defect in CD4+ T-cell production in HIV infection. Modeling of the CD4+ and CD8+ T-cell kinetics indicates the presence of one pool of cells with rapid turnover and one with slower turnover. For the rapidly dividing pool, the size of the pool was found to be closely correlated with plasma HIV-1 RNA levels.

There is ongoing debate over whether the observed CD4+ T-cell count decline in HIV infection is attributable to decreased T-cell production or increased T-cell death. The finding that T-cell production is considerably higher and correlated with plasma HIV-1 RNA levels in untreated infection, however, indicates that the primary mechanism of depletion is increased T-cell death (whether through direct cytopathic effects of HIV or activation-induced death). The increase in the CD4+ T-cell pool observed with potent therapy appears to be due to a decrease in cell death that more than compensates for the decreased production during therapy. The conclusion that can be drawn is that HIV infection leads to a state of immune activation and increased T-cell production inadequate to compensate for cell death, and that potent antiretroviral therapy immediately reverses the virus-driven increased T-cell production and reduces the polyclonal activation associated with functional immunosuppression. This conclusion helps explain the rapid improvement in opportunistic illnesses and the immune reactivation syndromes observed with potent antiretroviral therapy.

This conclusion also provides a mechanism other than increased thymic output to account for the increases in T-cell receptor rearrangement excision circles (TRECs) with potent antiretroviral therapy. TRECs are a circularized form of DNA, created by DNA excision during the process of T-cell receptor rearrangement in stem cells, that provides an index of thymic production of T cells. Since the TREC DNA is retained in only 1 daughter cell with each cell division, each round of cell divisions dilutes concentrations of TREC-containing cells by 50%. Thus, levels of TRECs in the T-cell pool are dependent on thymic cell output and rate of cell turnover.

A number of studies assessing T-cell dynamics using TREC measurements have shown that TREC levels are decreased in patients with HIV infection compared with uninfected controls and that TREC levels increase with initiation of potent antiretroviral therapy. Such data have been interpreted to indicate that thymic output is a major source of new cells following antiretroviral therapy and that T-cell production increases with the initiation of therapy. However, when change in TREC number is assessed as a function of change in T-cell turnover using BrdU labeling, a strong correlation is observed (Figure 2). These findings suggest that the increase in TREC number observed after treatment is more likely a reflection of the decreased cell turnover (and thus decreased dilution of the TREC pool) resulting from treatment rather than the product of increased thymic output.

### Evaluation of Host Immune Response

Immunologic control of viral infections is a crucial aspect of the host defense. Studies of the nature of the immune response to HIV are important in helping to better understand the pathogenesis of HIV infection and in developing immune-based therapies and vaccines. Host defense against viral infections utilizes both the innate and the adaptive elements of the immune system. As evidenced by the failure of the immune system to rid the host of HIV, the host responses are inadequate to successfully deal with this pathogen.

Understanding the host factors responsible for the control of viral infection remains an elusive goal. Various studies have examined the roles of HIV-specific CD8+ and CD4+ T cells in the response to HIV infection, but it is still the case that the best way to measure the host immune response to HIV infection is to measure the plasma level of HIV-1 RNA in the absence of treatment. This relatively simple technique affords the ability to examine the net result of all the various host factors that can control viral replication. Following primary

---

**Figure 2.** Correlation between change in rates of naive T-cell turnover (fold change in percentage of bromodeoxyuridine [BrdU]-positive naive cells) and change in concentration of T-cell receptor rearrangement excision circles (TRECs) in naive T cells ($R^2=0.96; P<0.001$). Adapted with permission from Lempicki et al, Proc Natl Acad Sci USA, 2000.
infection, a virologic set-point is reached that is difficult, if not impossible, to reduce once established. Studies in patients stopping potent antiretroviral therapy who had maintained plasma HIV-1 RNA levels at less than 50 copies/mL for periods of 1 to 4 years showed that plasma HIV-1 RNA generally returned to pretreatment levels with cessation of treatment (Figure 3). Such findings suggest that even prolonged periods of viral suppression appear to have little effect on host ability to control viral replication.

Although the determinants of the viral set-point remain unclear, 2 primary candidates are the size of the initial HIV reservoir and the number of HIV-specific T cells. A study by Davey and colleagues (Proc Natl Acad Sci USA, 1999) showed that the majority of patients discontinuing effective potent therapy exhibited dramatic viral rebound. Patients who exhibited lower levels of viremia were those in whom treatment was started soon after primary infection. This accords well with data from a study by Rosenberg and colleagues (Nature, 2000) suggesting that very early treatment may alter the viral set-point. An explanation is that early treatment shuts down viral replication before a larger viral reservoir (which would result in higher replication with removal of drug treatment) can be established. A second factor that may limit the size of the viral reservoir is host genetic background. For example, although the significance of the finding remains unclear, accumulating data suggest that a majority of patients who are long-term nonprogressors with low viral load (<50 HIV-1 RNA copies/mL) off treatment exhibit the human leukocyte antigen (HLA)-B57 haplotype (Migueles et al, Proc Natl Acad Sci USA, 2000). Similarly, polymorphisms in chemokine receptors may play an important role (O’Brien et al, Annu Rev Genet, 2000).

With regard to the role of HIV-specific CD8+ T cells in determining viral set-point, there is every reason to believe that these cells are important to the control of HIV infection. They have been shown to be essential for viral control in a variety of animal model systems, and have been found to exhibit a range of effector functions, including cytolytic activity, when exposed to HIV or HIV antigens. However, their specific role in host immune control of HIV infection remains unclear. CD8+ T cells reactive to HIV antigens decrease in number during prolonged effective antiretroviral therapy; when therapy is stopped, cell number rapidly increases without necessarily leading to a spontaneous suppression of plasma HIV-1 RNA level. These findings suggest that although the increase in levels of HIV-specific CD8+ T cells in the peripheral blood on stopping therapy is virus-driven, this increase is not necessarily indicative of a response that is effective in controlling the virus. Given what is known about the activity of these cells, the findings also suggest that it is unlikely that the number of these cells in the peripheral blood reflects the total body activity of the cells.

Similarly, it is difficult to draw conclusions regarding the effects of HIV-specific CD4+ T cells on viral control on the basis of currently available data. Although scientists initially believed that HIV-specific CD4+ T cells were preferentially depleted in HIV infection, recent data suggest that at least some subsets of cells with specificity for HIV antigens persist in chronic infection—although the role they may play in viral control is uncertain. One recent study (McNeil et al, Proc Natl Acad Sci USA, 2001) has shown that CD4+ T-cell responses, as measured by the HIV p24 antigen-specific lymphoproliferative assay, which reflects responses in relatively resting cells, are more likely to be present in patients on potent antiretroviral therapy. Assays that measure p24-induced interferon-γ reflect more activated HIV-specific CD4+ T cells (Figure 4). Cessation of therapy results in increased HIV-1 RNA levels, decreased lymphoproliferative responses, and increased interferon-γ-producing responses. Consideration of both assay results suggests that HIV-specific CD4+ T cells are present but have shifted from a predominantly resting to a predominantly activated state with cessation of therapy. With resumption of therapy, lymphoproliferative response increases and interferon-γ-producing response decreases somewhat.

In this and other studies, it is consistently observed that the proliferative capacity of HIV-specific CD4+ T cells, as well as that of CD4+ cells with specificities for non-HIV antigens, is compromised in the setting of high levels of HIV viremia. However, the clinical significance of these findings is unclear—a point recently underscored by the observation that despite the successful induction of CD4+ T-cell responses to p24 antigen by exogenous administration of HIV antigens in infected patients, there is no significant change in plasma HIV-1 RNA levels or progression to AIDS-defining events (Kahn et al, JAMA, 2000).

One area of research to determine how host immune response may be manipulated to complement the success of antiretroviral therapy is that of

![Figure 3. Levels of plasma viremia before initiation of potent antiretroviral therapy and after cessation of therapy in 14 patients in whom plasma HIV-1 RNA level was maintained at lower than 50 copies/mL for 1 to 4 years. Solid black lines indicate patients; dashed green line indicates mean. Adapted with permission from Hatano et al, AIDS, 2000.](image-url)
immune-based therapies. Studies of the effects of a 5-day cycle of interleukin-2 treatment in HIV-infected patients using DNA labeling have shown that treatment increases the percentage of dividing CD4+ T cells and increases the half-life of the cells (Kovacs et al., J Exp Med, 2001). The potential clinical effects of the increase in CD4+ T-cell production and, more importantly, the prolongation of cell survival with interleukin-2 treatment are being investigated in 2 large international phase 3 trials (SILCAAT and ESPRIT).

**Summary**

The immune systems of patients with HIV infection are characterized by polyclonal activation and immunodeficiency. The magnitude of the polyclonal activation appears to be directly related to the level of HIV viremia. Potent antiretroviral therapy leads to immediate improvement in the degree of activation and in many of the clinical manifestations of HIV infection. The recovery of T-cell numbers is a slower process and is likely driven by peripheral expansion rather than thymic output. Although CD4+ and CD8+ T cells that respond to HIV antigens can be identified, their precise role in host defense against HIV remains unclear. The single best measure to evaluate host immune response to HIV remains the plasma HIV-1 RNA level in the absence of therapy.

Presented in March 2002. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr. Lane in June 2002.

**Financial Disclosure** Dr. Lane is co-inventor on the patent for the use of interleukin-2 in HIV infection held by the US government.

**Suggested Reading**


Kovacs JA. Identification of dynamically distinct subpopulations of T lymphocytes that are differentially affected by HIV. [Abstract S10.] 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002; Seattle, Wash.


Mohri H, Perelson AS, Tung K, et al. Increased turnover of T lymphocytes in HIV-1 infection and
World Health Organization Guidelines for Scaling Up Antiretroviral Therapy in Resource-Limited Settings

The World Health Organization (WHO) issued draft guidelines in April 2002 for the scaling up of antiretroviral therapy in developing countries. The guidelines, written by an international group of experts, are intended to lower the technical barriers to treatment by recommending standardized regimens and simplified monitoring in resource-limited settings. Although applicable to the clinical practices of individual health care practitioners, the authors state that the recommendations are designed for senior-level policymakers in these settings.

The document includes guidelines for when to initiate and switch antiretroviral therapy, regimens for treatment-naïve and treatment-experienced patients, and treatment for pregnant women and children. Specific recommendations include:

- For adolescents and adults, antiretroviral therapy should be initiated based on WHO stage of HIV disease; for those without clinical AIDS, CD4+ cell count if available or total lymphocyte count. For children, antiretroviral therapy should be initiated based on WHO pediatric stage of HIV disease and, if possible, virologically proven infection (by HIV polymerase chain reaction, immune complex dissociated HIV p24 antigen detection, or HIV culture); for those without clinical AIDS or for whom virologic confirmation is not possible, CD4+ cell percentage.

- In adolescents and adults, the initial regimen should consist of a dual nucleoside reverse transcriptase inhibitor (nRTI) backbone plus 1 additional drug (i.e., efavirenz or nevirapine, abacavir, or a ritonavir-boosted protease inhibitor or nelfinavir). Regimens consisting of 2 nRTIs only are not recommended. In children, 2 nRTIs and a nonnucleoside reverse transcriptase inhibitor or abacavir are recommended (although efavirenz for children younger than 3 years old is not recommended).

- For pregnant women and women with the potential to become pregnant, zidovudine, lamivudine, nevirapine, nelfinavir, or saquinavir/ritonavir are recommended as possible components of an antiretroviral regimen.

- Because viral load tests are not usually available in resource-limited settings, clinical and, where possible, CD4+ cell count criteria should be used to define treatment failure.

- When treatment failure occurs, all of the drugs in the current regimen should be switched, ideally to at least 3 new drugs with at least 1 drug from a new class. This recommendation recognizes the reality that drug resistance testing is not routinely available for individualized patient management in resource-limited settings.

- Countries that implement antiretroviral therapy programs are encouraged to consider monitoring for drug resistance on a population level as therapy is introduced on a broad scale. This can be done through participation in the recently announced WHO-International AIDS Society Global HIV Drug Resistance Monitoring Project.

- Laboratory tests are prioritized into 4 categories: “absolute minimum,” “basic recommended,” “desirable,” and “optional.” The absolute minimum tests are defined as an HIV antibody test and a hemoglobin or hematocrit level. CD4+ count is included in the desirable category and viral load testing in the optional category. The need for low-cost, widely available laboratory assays for CD4+ cell and viral load monitoring is emphasized.

The WHO estimates that at least 6 million people in the developing world currently need antiretroviral therapy, and that fewer than 5% of those have access to treatment. The organization proposes that by the end of 2005, 3 million people should be receiving antiretroviral therapy.

The document, “Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Guidelines for a Public Health Approach,” is available online at:

www.who.int/HIV_AIDS

Copies may also be ordered by e-mail request to hiv-aids@who.int. For the most recent treatment recommendations by the International AIDS Society-USA, see the insert in this issue of Topics in HIV Medicine or visit www.iasusa.org for a link to JAMA.
Perspective
HIV Vaccine Research: Problems and Progress

At the Chicago International AIDS Society-USA course in April 2002, Richard A. Koup, MD, reviewed ongoing efforts to develop prophylactic anti-HIV vaccines. Among the approaches he discussed were vaccines that induce neutralizing antibodies to HIV and those that employ cytolysic T lymphocytes.

The urgent need for effective anti-HIV vaccines is most immediately felt when considering the scope of the HIV pandemic in such regions of the world as Africa, Southeast Asia, and China. Figure 1 shows HIV seroprevalence in South Africa from 1990 through 1999; in some areas of sub-Saharan Africa, HIV seroprevalence rates currently approach 50% (Schwartlander et al, Science, 2000). Figure 2 shows the projected population structure of Botswana in 2020 as it reflects the effects of AIDS deaths. Most HIV infections in the world occur in areas where antiretroviral therapy is unavailable or has only recently become available in some measure. In any case, antiretroviral therapy does not cure HIV infection. Population-based methods for preventing the spread of HIV infection are needed everywhere in the world.

Objectives in Vaccine Development

Based on the current understanding of HIV infection and immune response to infection, there are a number of potential immune correlates to be investigated in vaccine development (Letvin, J Clin Invest, 2002; Letvin et al, Annu Rev Immunol, 2002; Mascola and Nabel, Curr Opin Immunol, 2001). Vaccines may be used to stimulate antibodies that could bind virus and to neutralize or stop virus from infecting target cells, thereby eliminating free virus before cellular infection is established. Vaccines could also be employed to increase cytolysic T-lymphocyte (CTL) responses targeting virus-infected cells or to stimulate antiviral factors elaborated by these cells. In the case of HIV infection, the ability to elicit or augment immune responses at locations in addition to the circulation may be of importance; since HIV enters the body at mucosal surfaces and replicates in lymphoid tissue, induction of immune response at these sites may be necessary as preventive approaches.

There are different levels or types of protection at which vaccine development can be aimed. In sterilizing immunity, infection is never established, and there is no seroconversion to nonvaccine antigens, no detectable HIV in the host at any time, and no risk of transmission of HIV to others. Although this is a desired goal, no vaccine against any human pathogen has ever stimulated sterilizing immunity. A successful vaccine might permit transient infection, in which there is transient detection of HIV at mucosal sites or in the blood but no detectable virus at later time points (eg, 6-12 months) with maintenance of immune response. HIV seroconversion might or might not occur, and risk of transmission of infection might be time-limited or completely prevented. Vaccines might also result in long-term controlled infection, in which virus is detectable or at very low levels throughout life and in which there is no harmful drop in CD4+ cell count and no immunodeficiency disease. Seroconversion in this case is likely, and risk of transmission might be prevented or greatly reduced. Another potential aim of vaccine development, albeit a relatively undesirable one, might be an “altruistic” vaccine. In this case, the vaccine might provide no protection from infection or disease in those vaccinated, but would reduce viral load in mucosal secretions such that risk of transmission would be reduced or eliminated.

Is Vaccine-Induced Immunity Against HIV Possible?

There are a number of reasons to be optimistic about the potential for inducing immunity to HIV. HIV transmission is relatively inefficient. The primary mode of transmission worldwide is sexual, and transmission usually occurs only after

---

Dr Koup is Chief of the Immunology Laboratory at the National Institutes of Health Vaccine Research Center, Bethesda, Md.

---

multiple exposures (Downs and De Vincenzi, J Acquir Immune Defic Syndr Hum Retrovirol, 1996; Mastro and Kitayaporn, AIDS Res Hum Retroviruses, 1998). It is known that only a small number of viruses establish infection during exposure (Zhu et al, Science, 1993); the likelihood that inoculum size is a factor in transmission suggests that reduction of the inoculum through vaccination might prevent infection. Transmitted viruses may have limited structural and genotypic features, reducing the genetic variability that would need to be covered by an effective vaccine. In addition to these factors, there are examples of natural immunity to infection that suggest that prevention is possible, including highly exposed individuals who remain uninfected and individuals with long-term nonprogressive infection (Cao et al, N Engl J Med, 1995; Rowland-Jones et al, Nat Med, 1995). Individuals with HIV-2 infection do not exhibit rapidly progressive disease, and they may have some degree of protection against HIV-1 infection (Travers et al, Science, 1995). Finally, there is evidence of vaccine-induced protection in animal models—eg, the simian immunodeficiency virus (SIV) macaque model (Amara et al, Science, 2001; Barouch et al, Science, 2000).

Although there is reason for optimism regarding the ability to induce immunity, there are also substantial biological challenges facing vaccine development (Letvin et al, Annu Rev Immunol, 2002). HIV infection is characterized by early establishment of cellular integration and latency; once infection occurs, latency is very likely and elimination of the virus is improbable. The virus preferentially infects and depletes key immune mediators (Douek et al, Nature, 2002), including CD4+ T-helper cells and antigen-presenting cells. HIV has other immune evasion strategies: HIV Nef downregulates major histocompatibility complex (MHC) class I expression, potentially interfering with immune recognition of HIV-infected cells; the immune response to infection includes failure to mount a good neutralizing antibody response; and a wide genetic variation in the virus population in established infection enables the virus to escape host immune responses.

Inducing Neutralizing Antibody Response

It is difficult to induce broadly reactive neutralizing antibodies to HIV by immunization. The HIV envelope glycoprotein features loop domains with high variability, which permit the virus to evade antibody recognition. The envelope is also heavily glycosylated, with the glycosylation moieties shielding the regions of the envelope protein gp120 that are targeted by neutralizing antibodies. The conformational changes in gp120 during CD4 binding reveal the viral binding site for the cellular CCR5 coreceptor; although this domain of gp120 is a potential antibody target, access may be blocked by steric hindrance. The gp120 is also a flexible protein, which makes it a more difficult target for antibodies than a rigid protein would be. The conformational change that occurs in the envelope glycoprotein gp41 during binding reveals additional epitopes that can serve as antibody targets; monoclonal antibodies targeting these regions of gp41 are being developed in the attempt to prevent fusion of virus with target cell membrane. HIV exhibits rapid escape from neutralizing antibodies, and continual escape from these antibodies is observed in individuals with chronic HIV infection.

There are reasons to be optimistic about inducing immunity to HIV, but there are also substantial biological challenges in vaccine development

Studies with vaccines to induce neutralizing antibodies generally have shown that the antibody produced in animals or human subjects exhibits high neutralization titers against laboratory (T-cell-line-adapted) HIV but poor titers against primary HIV isolates from infected individuals (Mascola et al, J Infect Dis, 1996). For example, investigation in human subjects of the recombinant ALVAC vaccine, a vaccinia-like vaccine
that expresses gp120, showed that all of the neutralizing antibodies generated in response to vaccination were type-specific and that response was of relatively short duration (Belshé et al, AIDS, 1998). The neutralizing titers were 5 to 10 times lower than sera from individuals with long-term nonprogressive HIV infection, and the antibody did not neutralize primary HIV isolates.

A number of strategies for improving neutralizing antibody responses are being pursued. These include attempts to improve protein expression in vaccines, unmask the neutralizing antibody epitopes on gp120 by removing the glycosylation sites that shield the neutralizing domain or removing the variable loop domains of the glycoprotein, express native trimeric forms of gp41 and gp120, express a rigid (neutralization-sensitive) form of gp120, and express a fusion-competent form of the glycoprotein.

**CTL-Based Vaccines**

Among the advantages of a CTL-based vaccine approach is the fact that CTLs recognize HIV-infected cells. Although antibodies would be expected to have their primary effect on free virus, they may also be used to target productively infected cells and promote elimination of these cells through activity of complement or targeting by other natural killer cells. If latently infected cells express some viral protein, it is also possible that this approach could have an effect on the latent HIV reservoir. Overall, targeting of HIV using a CTL-based approach may be more efficient than with antibodies, since CTLs recognize multiple linear epitopes.

The reliance of the CTL-based vaccine approach on recognition of HIV-infected cells, however, may also constitute a disadvantage, since the antiviral effect would only occur after cellular infection had taken place. Other potential disadvantages include the requirement that active memory cells be present in sufficient amounts, the potential downmodulation of MHC by HIV that can enable infected cells to escape detection, and the fact that access to infection sites is more limited for CTLs than for antibodies.

Evidence that CTLs are important for control of HIV and SIV includes a negative correlation between CTL numbers and viral load (Ogg et al, Science, 1998), an increase in SIV viremia observed with CD8+ cell depletion in the SIV-infected macaque model (Jin et al, J Exp Med, 1999; Schmitz et al, Science, 1999), and an association between the appearance of CTL activity and a decline in HIV viremia in acute infection (Borrow et al, J Virol, 1994; Koup et al, J Virol, 1994). Studies in HIV-infected individuals have shown that 2% to 20% of total CD8+ cells are specific for HIV antigens, suggesting a strong CTL response (Betts et al, J Virol, 2001).

**Status of Vaccine Development**

Traditional approaches to viral vaccine development have consisted of using live, attenuated virus or whole, killed virus. There are safety concerns with the former approach for HIV vaccines in that the live, attenuated forms of HIV or SIV that have been tested appear to be pathogenic (Baba et al, Nat Med, 1999; Greenough et al, N Engl J Med, 1999). There are also safety concerns with the use of whole, killed virus, in addition to concerns regarding the potential lack of adequate production of CTL using this approach. Most HIV vaccines currently in development are the products of recombinant DNA technology. In this approach, DNA encoding 1 or more viral proteins can be used to transfect cells in the laboratory to produce antigen that can be used as a vaccine. The DNA can also be delivered as a vaccine through a viral vector, such as vaccinia virus or adenovirus, with the antigens thus being expressed in vivo. The DNA can also be directly injected (ie, the "naked" DNA approach) to stimulate in vivo antigen production.

Selected vaccine strategies that are currently being tested in clinical trials are shown in Table 1. A gp120 envelope subunit vaccine is currently in phase 3 evaluation. A canarypox-vector vaccine is in phase 2 testing. Vaccines using adenovirus-vector, DNA, vaccinia-vector,
and peptide approaches are in phase 1 or phase 1/2 evaluation. The final results of the phase 3 trial of the gp120 subunit vaccine are due in the fall of 2002; expectations are not high that the vaccine will prove to be protective, particularly since the gp120 used in the vaccine is monomeric and the vaccine does not appear to be effective in inducing neutralizing antibodies. A canarypox-vector vaccine was assessed by the Human Vaccine Trials Network of the National Institutes of Health (NIH) and did not produce levels of immunogenicity deemed adequate to warrant going forward with phase 3 trials; nevertheless, this vaccine is being examined in the phase 3 setting by the US Army (Cohen, Keystione Symposium, 2002). A modified-vaccinia-Ankara-based vaccine strain is currently being examined in both phase 1 and phase 2 studies.

A vaccine in which Gag-DNA administration is followed by an adenovirus boost has produced intriguing results in animal studies. The aim of this vaccine is to induce pure cellular immunity rather than to induce neutralizing antibody response; although the vaccine currently being tested expresses Gag protein, it could be modified to contain CTL responses with cross-HIV clade recognition have also been stimulated, and it appears that preexisting immunity to the adenovirus vector can be overcome by increasing the dose of adenovirus in the vaccine (Emini, Keystone Symposium, 2002). The vaccine was found to be partially protective against challenge with simian-human immunodeficiency virus. The NIH Vaccine Research Center is also pursuing a strategy of DNA followed by adenovirus. The vaccine currently being tested uses a construct of clade-B HIV Gag and Pol. In a dose-escalation trial examining the safety and immunogenicity of this vaccine, 3 groups of 7 patients each are to receive 3 doses of 0.5, 1.5, or 4.0 mg via a needle-free injection system, with 2 patients receiving placebo at each dose level. Future Vaccine Research Center initiatives are to involve additional viral antigens (eg, Gag, Pol, Nef, and Env), envelope modifications, and antigens from clade A, B, and C viruses; use of a prime/boost method for the adenovirus vector; and use of cytokine adjuvants to increase T-cell memory.


Financial Disclosure: Dr Koup has no affiliations with commercial organizations that may have interests related to the content of this article.

The DNA/adenovirus approach is promising because it has stimulated the strongest and most cross-reactive T-cell immunity

Suggested Reading


Burton DR, Montefiori DC. The antibody response in HIV-1 infection. AIDS. 1997;11(suppl A):S87-S98.


Perspective
Current Status of New Antiretroviral Drugs in Development

At the International AIDS Society–USA course in Washington, DC, in May 2002, Roy M. Gulick, MD, MPH, discussed characteristics of select investigational antiretroviral drugs, including new reverse transcriptase and protease inhibitors and drugs that inhibit HIV entry and integration.

Currently, 16 antiretroviral drugs are approved for treatment of HIV infection. However, even the best currently available regimens pose challenges with regard to adherence, toxicity, antiviral activity, and resistance. New drug development thus confronts the need for improved convenience and tolerability, reduced toxicity, and improved activity against both wild-type and drug-resistant viruses. Other goals of drug development include improved drug penetration into viral reservoirs (eg, genital tract and central nervous system) and exploitation of additional viral targets with the aims of achieving additive or synergistic effects with drugs from existing classes, reducing or preventing viral resistance, and improving treatment options in cases of drug resistance.

Newly available or investigational formulations or doses of existing nucleoside reverse transcriptase inhibitors (nRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) are shown in Table 2; select drugs from this listing are discussed herein. Figures 1 and 2 show the HIV-1 life cycle and the stages of the life cycle targeted by available drug classes and by drugs from newer and investigational classes such as entry inhibitors and integrase inhibitors.

HIV Nucleoside Reverse Transcriptase Inhibitors

Amdoxovir

Amdoxovir (DAPD) is an investigational guanine analogue active in vitro against both HIV and hepatitis B virus. Pharmacokinetic data support twice-daily dosing of the compound. Amdoxovir is active in vitro against zidovudine-resistant and lamivudine-resistant virus and some multidrug-resistant strains with the reverse transcriptase codon 69 insertion. The reverse transcriptase mutations K65R and L74V reduce susceptibility to the compound in vitro. The K103N mutation associated with efavirenz resistance may be associated with hypersensitivity to amdoxovir. In animal toxicity studies, the compound produced an obstructive nephropathy, caused by crystallization of the compound in the renal tubules, that led to hyperglycemia and cataracts in some animals.

In an initial study in 24 patients who had received prior zidovudine or stavudine and prior lamivudine, amdoxovir was given at 200 mg, 300 mg, or 500 mg twice daily after drug washout or at 500 mg twice daily in addition to the patients' current regimen (Raffi et al, 5th Int Cong Drug Ther HIV Infect, 2000). In patients undergoing drug washout, amdoxovir 500 mg twice daily reduced plasma HIV-1 RNA level by a median of 1 log10 copies/mL at 15 days, with smaller reductions observed at lower doses. The addition (without washout) of amdoxovir to background treatment produced a median 2-log10 decrease in plasma HIV-1 RNA level, although the reason for this greater decrease is not clear. Mycophenolic acid inhibits inosine 5’-monophosphate dehydrogenase and thereby depletes intracellular dGTP levels, thus enhancing the in vitro antiviral activity of guanosine nucleoside analogues such as abacavir and amdoxovir (Margolis et al, J Acquir Immune Defic Syndr Hum Retrovirol, 1999; Ying et al, Antiviral Res, 2000). Phase 2 studies of amdoxovir, both with and without mycophenolic acid, are in progress.

HIV Nonnucleoside Reverse Transcriptase Inhibitors

BMS 56,1390 (DPC-083)

A number of NNRTIs that are structurally related to efavirenz have been developed, and the leading clinical candidate is BMS 56,1390. Phase 2 studies of BMS 56,1390 have shown promising results in terms of efficacy and safety.

Table 1. New Formulations and Dosing Strategies of Existing Antiretroviral Drugs

HIV Nucleoside Reverse Transcriptase Inhibitors

- zidovudine bid dosing*; controlled-release formulation qd
- didanosine enteric-coated capsule qd*
- zalcitabine bid
- stavudine extended release 100 mg qd
- lamivudine qd*
- lamivudine/zidovudine fixed-dose combination*
- lamivudine/zidovudine/abacavir fixed-dose combination*
- lamivudine/abacavir fixed-dose combination

HIV Nonnucleoside Reverse Transcriptase Inhibitors

- delavirdine 200-mg tablet*
- efavirenz 600-mg capsule*

HIV Protease Inhibitors

- saquinavir soft-gel formulation*; 800-mg hard-gel capsule
- nelfinavir bid dosing*; 625-mg tablet
- ritonavir enhancement of saquinavir, indinavir, or amprenavir*
- lopinavir/ritonavir coformulation*
- GW433908 (amprenavir prodrug VX-175)

* Currently approved by the US Food and Drug Administration.

Dr. Gulick is Associate Professor of Medicine at Weill Medical College of Cornell University and Director, Cornell University HIV Clinical Trials Unit, New York Presbyterian Hospital, New York.
is BMS 56,1390 (formerly DPC-083). This compound exhibits good oral bioavailability and has a half-life of greater than 90 hours, supporting once-daily and perhaps less frequent dosing. The compound undergoes metabolism via the cytochrome P450 (CYP) 3A4 and 2B6 hepatic isoenzyme systems. Compared with efavirenz, BMS 56,1390 exhibits 3-fold greater activity in vitro against K103N mutants and some double mutants. Resistance in vitro appears to require the presence of more than 1 reverse transcriptase mutation. The compound currently is in phase 2 and 3 evaluation.

In a recently reported study, 134 treatment-naive patients with an average plasma HIV-1 RNA level of 33,000 copies/mL and CD4+ cell count of 402/µL received fixed-dose lamivudine/zidovudine at the standard dose plus efavirenz 600 mg or BMS 56,1390 at 50 mg, 100-mg, or 200-mg once-daily doses. In an intent-to-treat analysis, 60% to 70% of patients in the 4 arms had plasma HIV-1 RNA level reduced to less than 50 copies/mL at 16 weeks (Ruiz et al, Abstract 6, 9th CROI, 2002).

In another study, 75 NNRTI-experienced/PI-naive patients in whom current therapy was failing received 2 nRTIs selected on the basis of genotypic analysis and BMS 56,1390 at 100 mg or 200 mg once daily (Ruiz et al, Abstract 7, 9th CROI, 2002).

TMC 125

TMC 125 is an investigational NNRTI that exhibits antiretroviral activity in vitro against a high proportion of clinical HIV isolates with resistance to nevirapine, delavirdine, or efavirenz. A study in treatment-naive, HIV-infected patients with an average baseline HIV-1 RNA level of 58,000 copies/mL and CD4+ cell count of 650 cells/µL, TMC 125 900 mg twice daily given as monotherapy produced a 2-log10 reduction in plasma HIV-1 RNA level in 12 patients at 7 days, compared with no change in 7 placebo recipients (Gruzdev et al, 41st ICAAC, 2001).

A study in 16 NNRTI-experienced patients (prior nevirapine in 81% and prior efavirenz in 19%) with an average plasma HIV-1 RNA level of 16,000 copies/mL and a CD4+ cell count of 464/µL, TMC 125 900 mg twice daily reduced mean plasma HIV-1 RNA level by nearly 1 log10 from the baseline value (Gazzard et al, 9th CROI, 2002). Further studies are in progress. The blunted antiretroviral response in NNRTI-experienced subjects compared with NNRTI-naive subjects in these pilot studies suggests that some degree of resistance is conferred by NNRTI-associated mutations. This concern supports the early discontinuation of currently available NNRTI-based regimens after confirmed virologic failure, in order to avoid the accumulation of additional NNRTI-associated mutations that may compromise the activity of investigational NNRTIs, including TMC 125.

HIV Protease Inhibitors

Atazanavir

Atazanavir is an azapeptide PI in development. It exhibits a 90% inhibitory concentration (IC90) for HIV in vitro of 60 to 80 nM (adjusted for protein binding).
Pharmacokinetic data support once-daily dosing, which would make the compound unique among currently approved PIs without ritonavir boosting; the proposed dose is two 200-mg pills with food once daily. The drug is metabolized by the CYP 3A4 hepatic enzyme system. Adverse effects include an indirect hyperbilirubinemia, similar to that observed with indinavir. Minimal or no lipid changes have been observed with administration of the drug in clinical studies.

Atazanavir is in phase 3 testing. It is also currently available through an expanded-access program for patients with CD4+ cell count less than 300/µL and plasma HIV-1 RNA level greater than 5000 copies/mL, or with any viral load if triglyceride or total cholesterol levels are greater than 750 mg/dL and the patient is not responding to lipid-lowering therapy. Information about the expanded access program is available by calling 1-877-726-7327.

In a phase 3 study in 467 treatment-naive patients with a plasma HIV-1 RNA level greater than 2000 copies/mL and a CD4+ cell count greater than 75/µL, stavudine/lambda was given with atazanavir at a daily dose of 400 mg (n=181) or 600 mg (n=195) or nelfinavir 1250 mg twice daily (n=91; Sanne et al, 41st ICAAC, 2001). In an intent-to-treat analysis, approximately 65% had a plasma HIV-1 RNA level less than 400 copies/mL and approximately 40% of patients in each arm had a level less than 50 copies/mL at 48 weeks. Overall, virologic response rates in both arms of this study were somewhat lower than other phase 3 studies of PIs, including nelfinavir, for unclear reasons. There was a significant difference in the change in total cholesterol levels between the groups, with an approximate 25% increase from baseline observed in the nelfinavir group compared with a 5% increase in the atazanavir groups by week 48.

In another study in patients failing current therapy, 85% of whom had received prior PI treatment, 85 patients with a plasma HIV-1 RNA level of 2000 to 100,000 copies/mL and a CD4+ cell count greater than 100/µL received atazanavir 400 mg or 600 mg plus saquinavir 1200 mg once daily, or ritonavir 400 mg plus saquinavir 400 mg twice daily. Of note, saquinavir and atazanavir exhibit a pharmacokinetic interaction that increases blood levels of both drugs. Analysis of observed data in a total of 51 patients at 48 weeks showed that all 3 treatment regimens were associated with median reductions in viral load of approximately 1.2 to 1.6 log10 (Haas et al, 9th CROI, 2002).

Figure 1. The life cycle of HIV-1. At left, the virion is shown attaching to the CD4 receptor and chemokine coreceptor and subsequently entering the host CD4 cell. Inside the cell, transcription of HIV RNA to HIV DNA is catalyzed by the HIV reverse transcriptase enzyme. The HIV DNA then forms a double-stranded DNA (dsDNA) complex, enters the host cell nucleus and integrates with the host genetic material via the HIV integrase enzyme. Upon activation, the viral DNA is transcribed into viral messenger RNA (mRNA) that in turn is translated into viral precursor proteins. The new HIV RNA and viral precursor proteins are assembled and the virus buds and is released from the cell surface. After budding, viral precursor proteins undergo processing by the HIV protease enzyme and form a mature, infectious viral particle.
Tipranavir

Tipranavir is a nonpeptidic investigational PI with a 90% effective concentration (EC90) of 0.5 to 1.0 µM for HIV in vitro. It is active in vitro against a large majority of clinical HIV isolates resistant to indinavir, ritonavir, nelfinavir, and saquinavir. Coadministration with ritonavir increases trough tipranavir concentrations by 7- to 40-fold, allowing the compound to be dosed twice daily, and absorption is increased if the drug is taken with a high-fat meal. The compound has been developed with a new self-emulsifying drug delivery system (SEDDS). It is metabolized via the CYP 3A4 hepatic enzyme system. Tipranavir currently is in phase 1/2 testing.

Tipranavir was evaluated in a pilot study in patients in whom treatment with 1 PI had failed. Enrollment criteria were baseline plasma HIV-1 RNA level greater than 1000 copies/mL and any CD4+ cell count. Sixty-two patients received one of 2 regimens: 2 new nRTIs with either tipranavir 500 mg or 1250 mg twice daily plus ritonavir 100 mg twice daily, or saquinavir (soft gel capsule) 400 mg plus ritonavir 400 mg twice daily. Intent-to-treat analysis showed that approximately 60% of patients receiving tipranavir regimens and approximately 50% of those receiving the saquinavir regimen had a greater than 1-log10 decrease in plasma HIV-1 RNA level at 16 weeks (Slater et al, 41st ICAAC, 2001). The effectiveness of tipranavir in PI-experienced patients requires further evaluation.

TMC 114

TMC 114 demonstrates in vitro activity against a majority of clinical HIV isolates with resistance to saquinavir, indinavir, ritonavir, nelfinavir, and amprenavir. The first study of this investigational PI in healthy volunteers has been reported and studies in HIV-infected patients are under way.

HIV Entry Inhibitors

HIV entry inhibitors (CD4) cells by initially binding to the CD4 receptor (Figure 1). Interaction with the CD4 receptor induces a conformational change in the HIV gp120 that allows binding to a second receptor, the chemokine coreceptor (CCR5 and/or CXCR4). This induces another conformational change in the HIV gp41 protein, bringing the viral and cell surfaces into contact. Fusion of the viral and cell membranes completes viral entry. Candidate drugs for blocking HIV entry thus include CD4 attachment inhibitors, chemokine coreceptor inhibitors, and fusion inhibitors (Figure 2).

SCH-C

SCH-C (SC-351125) is a small-molecule binder of the CCR5 chemokine coreceptor with in vitro activity against HIV strains using the CCR5 coreceptor (IC50 ~20 nM) and against hybrid strains using both the CXCR4 and CCR5 coreceptors. Although there is a theoretical concern that a CCR5 inhibitor could promote a switch to the CXCR4 coreceptor (present with more virulent X4 viral strains), in mouse studies, emergence of resistance to SCH-C did not result in coreceptor switch (Moore, 1st IAS Conf on HIV Pathog and Treat, 2001). SCH-C is orally bioavailable, and pharmacokinetic data indicate a half-life of 4 to 6 hours, supporting twice-daily dosing. The mechanisms of metabolism of the drug have not been fully defined, but they do not appear to involve cytochrome P450 hepatic metabolism. In a phase 1 dose-escalation study in healthy volunteers given single doses of SCH-C, a prolongation (>50 msec) of the QTc interval was observed in 1 subject at the highest dose tested, 600 mg. In a phase 1 study in 28 HIV-infected patients, treatment with SCH-C 25 mg

Figure 2. Stages of the HIV-1 life cycle targeted by currently approved and new investigational classes of anti-HIV drugs. The dsDNA indicates double-stranded DNA; mRNA, messenger RNA.
Enfuvirtide

Enfuvirtide (T-20) is a peptide fusion inhibitor that is given subcutaneously at a proposed dose of 90 mg twice daily. Adverse effects are primarily injection site reactions. Resistance mutations to enfuvirtide have been observed in vitro and in vivo and appear to involve mutations in gp41.

In a phase 1 study (Kilby et al., Nat Med, 1998) in which 16 patients received 4 different intravenous doses for 14 days, a 2-log₁₀ decrease in plasma HIV-1 RNA level was observed at the highest dose. Activity of the subcutaneous formulation has been demonstrated in both phase 2 and 3 studies, and the drug is now available under an expanded-access program.

In 2 recently presented phase 3 studies, the use of enfuvirtide led to improved virologic suppression when added to an optimized antiretroviral regimen in treatment-experienced subjects (Henry et al., 14th Int AIDS Conf, 2002; Clotet et al., 14th Int AIDS Conf, 2002). In the TORO (T-20 vs optimized regimen only)-1 study, HIV-infected patients with at least 6 months of prior treatment experience with all 3 classes of available antiretroviral drugs and an HIV-1 RNA level of greater than 5000 copies/mL underwent both genotypic and phenotypic resistance testing and selected a new antiretroviral regimen. They were then randomized 2:1 to add enfuvirtide to the regimen (90 mg subcutaneously twice daily) or not. A total of 491 subjects were randomized with a baseline HIV-1 RNA level of 159,000 copies/mL and CD4+ count of 80 cells/µL. The subjects had taken an average of 12 prior antiretroviral drugs and 80% had demonstrated 5 or more primary resistance mutations to all 3 antiretroviral drug classes. At 24 weeks, an intent-to-treat, last-observation-carried-forward analysis demonstrated a highly significant mean change from baseline plasma HIV-1 RNA of −1.7 log₁₀ copies/mL (enfuvirtide plus optimized regimen group) versus −0.8 log₁₀ copies/mL (optimized regimen only group). The TORO-2 study of 504 patients demonstrated similar results. In both studies, the most common adverse experience was injection site reactions, but drug discontinuation for that reason was uncommon.

T-1249

T-1249 is structurally similar to enfuvirtide and was constructed by combining gp41 sequences from HIV-1, HIV-2, and simian immunodeficiency virus. The drug is also administered subcutaneously. T-1249 is 2 to 100 times more active against HIV in vitro than enfuvirtide and retains significant activity against enfuvirtide-resistant strains (Greenberg et al., Antivir Ther, 2002). Because enfuvirtide-associated resistance substitutions may confer some degree of cross-resistance to T-1249, consideration should be given to early discontinuation of enfuvirtide-containing regimens after virologic failure develops, to avoid the accumulation of additional substitutions. The investigational drug is currently in phase 1/2 evaluation.

In a phase 1/2 dose-escalation study, the area under the drug concentration-time curve and the minimum blood concentration were dose-proportional with once-daily dosing for 14 days. After a 4-week washout period, 63 patients received T-1249 6.25 mg, 12.5 mg, or 25 mg once or twice daily for 14 days. Sixty-two patients were antiretroviral-experienced, with prior exposure to an average of 10 drugs. At day 14, reductions in plasma HIV-1 RNA level were approximately 1.3 log₁₀ in the 25 mg twice-daily group, and 0.7 log₁₀ in the 25 mg once-daily group (Eron et al., 8th CROI, 2001). Data from additional studies of the drug should be available in the near future.

HIV Integrase Inhibitors

In addition to the HIV reverse transcriptase and protease enzymes, the third viral-specific enzyme is HIV integrase. This enzyme promotes 3 specific steps of HIV integration: (1) binding to the viral DNA complex; (2) processing of viral DNA; and (3) DNA strand transfer whereby viral DNA is inserted into host cell DNA (Figure 1). As a unique viral-specific enzyme, it is an attractive target for antiretroviral drug development (Figure 2).

S-1360

S-1360, a small-molecule HIV integrase inhibitor, is the first of the HIV integrase inhibitors to reach clinical testing. S-1360 has an EC₅₀ value of 0.025 to 0.074 µg/mL for HIV in vitro before protein binding. Pharmacokinetic data suggest that the drug can be dosed orally 2 or 3 times daily; it is greater than 99% protein bound and is not metabolized via the CYP 3A4 system. Emergence of resistance in vitro has been associated with novel mutations in the HIV integrase active site. Administration in healthy volunteers has produced few adverse effects. S-1360 is currently being evaluated in phase 1 studies in treatment-experienced HIV-infected patients with CD4+ cell counts greater than 100/µL (Yoshinaga et al., 9th CROI, 2002).

L-870812 and L-870810

In vitro, diketoacids demonstrated potent anti-HIV integrase activity as strand transfer inhibitors, but these negatively charged compounds were not clinical candidates. Modification of these compounds led to the identification of a series of compounds with improved antiretroviral potency and pharmacokinetic characteristics, including good oral bioavailability. In monkeys, L-870812 was administered orally as a single agent and demonstrated virologic suppression of 1 to 3 log₁₀ copies/mL and preserved CD4+ cell counts for a 75-day period (Hazuda et al., Antivir Ther, 2002). A related compound, L-870810, is currently under investigation in healthy volunteers, and studies in HIV-infected subjects are anticipated.

Conclusion

New antiretroviral drugs are needed to improve convenience, tolerability, safety, and antiviral activity of antiretroviral
therapy. Promising agents are in development in existing classes (ie, reverse transcriptase and protease inhibitors) and in new classes (eg, HIV entry and HIV integrase inhibitors). Additional steps in the viral life cycle, including viral uncoating and viral assembly, and other enzymes, such as RNAase H, can and should be targeted in future drug development. Additional approaches using immune therapies such as interleukin-2 and therapeutic HIV vaccines may complement the use of current and future antiretroviral agents. Further basic and clinical research aimed at identifying and developing promising antiretroviral agents is needed.


Financial Disclosure Dr Gulick has received grant support from or served as a consultant to or on the speakers bureau of Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Shionogi, Trimeris, and VircoLogic. His unit has also received unrestricted educational grants from numerous companies for an annual Cornell CME course held in November.

Suggested Reading

Baroudy B. Co-receptor inhibitors. [Abstract MoOAI38]; 14th International AIDS Conference. July 7-12, 2002; Barcelona, Spain.

Clotet B, Lazzarin A, Cooper D, et al. Enfuvirtide (T-20) in combination with optimized background (OB) regimen vs OB alone in patients with prior experience or resistance to each of the three classes of approved antiretrovirals (ARVs) in Europe and Australia. [Abstract LBOr19A.] 14th International AIDS Conference. July 7-12, 2002; Barcelona, Spain.


Gazzard B, Pozniak A, Arasteh K, et al. TMC125, a next-generation NNRTI, demonstrates high potency after 7 days therapy in treatment-experienced HIV-1 infected individuals with phenotype NNRTI resistance. [Abstract 4.] 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002; Seattle, Wash.


Gruzdiev B, Rakhmanova A, De Dier K, Comhaire F, Gilard M. Identification of amino acid substitutions correlated with reduced atazanavir susceptibility in numerous companies for an annual Cornell CME course held in November.


Hazarudin D, HIV-1 Integrase Inhibitor Discovery Team. A novel HIV-1 integrase inhibitor mediates sustained suppression of viral replication and CD4 depletion in a SHIV rhesus macaque model of infection. [Abstract 1.] Antivir Ther. 2002;7(suppl 1):S3.


Clinical Pathway Webcast: Lectures From the Ryan White CARE Act 2002 All Grantee Conference

About the Conference
The Ryan White CARE Act 2002 All Grantee Conference was held August 20 through 23, 2002, in Washington, DC. The Clinical Pathway, a 2-day series of lectures convened as part of the All Grantee Conference, was held August 20 and 21. The Clinical Pathway was supported by and conducted in collaboration with the HIV/AIDS Bureau of the Health Resources and Services Administration of the US Department of Health and Human Services and was sponsored by the International AIDS Society–USA.

Co-chaired by Laura W. Cheever, MD, and Michael S. Saag, MD, Clinical Pathway focuses on current clinical issues in HIV management. It is designed for physicians, physician assistants, and nurse practitioners who provide services in Ryan White CARE Act programs and are involved in direct HIV patient care.

About the Webcast
A Webcast of Clinical Pathway lectures is available on the IAS–USA Web site at:

www.iasusa.org

Minimum workstation requirements include Microsoft Windows 98 operating system, Internet Explorer 5.0, and Media Player. Lectures may be viewed using PCs and are not accessible by Macs.

Lectures and Speakers

Current Issues in Antiretroviral Therapy, Including HIV Pathogenesis and Clinical Challenges
Michael S. Saag, MD
The University of Alabama at Birmingham

Current Strategies for Defining and Managing Antiretroviral Failure
Roy M. Gulick, MD, MPH
Weill Medical College of Cornell University

Clinical Use of Resistance Testing
Daniel R. Kuritzkes, MD
Harvard Medical School

Making Sense of HIV Immunity
Paul A. Goepfert, MD
The University of Alabama at Birmingham

Global Epidemiology of HIV/AIDS
Thomas C. Quinn, MD
The Johns Hopkins University

The Diagnosis and Management of Hepatitis B and C Virus Infections in the HIV-Infected Patient
Raymond T. Chung, MD
Harvard Medical School

The Changing Nature of the Prevention and Management of HIV-Related Opportunistic Infections
Henry Masur, MD
National Institutes of Health

Reproduction and Women’s Health Issues
Erika Z. Aaron, CRNP
MCP Hahnemann School of Medicine

Substance Abuse in the HIV-Infected Population
Henry Francis, MD
National Institute on Drug Abuse

Common Medical Illnesses Associated With HIV Disease: Osteonecrosis, Osteopenia/Osteoporosis, and Hypertension
Meg D. Newman, MD
University of California San Francisco

Metabolic Complications: Insulin Resistance, Diabetes, and Fat Distribution
Constance A. Benson, MD
University of Colorado Health Sciences Center

Metabolic Complications: Lipid Abnormalities and Cardiovascular Disease Risk
Colleen M. Hadigan, MD, MPH
Harvard Medical School

Overcoming Depression in HIV
Andrew F. Angelino, MD
The Johns Hopkins University
The International AIDS Society–USA publishes Topics in HIV Medicine as a resource for physicians and other health care practitioners who are actively involved in HIV and AIDS care. The publication is distributed to approximately 12,000 national and international subscribers.

The following guidelines describe the types of articles and contributions published in the journal, outline its policies, and provide instructions for authors. For further information, contact Topics in HIV Medicine at topics@iasusa.org.

Categories of Articles

**Perspectives.** Perspectives articles are summaries of selected talks given at International AIDS Society–USA continuing medical education courses. An International AIDS Society–USA medical writer prepares a summary manuscript from a transcript of the talk. The manuscript is reviewed and edited by the specific course presenter and the journal’s appointed peer reviewers.

**Reviews.** Topics in HIV Medicine welcomes unsolicited original review articles on current issues in HIV and AIDS for consideration. Topics in HIV Medicine does not publish original research. Manuscripts should be 3000 to 6000 words (excluding references, tables, and figures) and should include numbered references and a brief introductory abstract of approximately 100 to 200 words. Original, adapted, or reprinted figures and tables may be included and should be cited in the text and accompanied by a brief title. Adapted and reprinted work requires the submission of permission obtained from the original publishers and authors. Authors interested in submitting unsolicited manuscripts are encouraged to submit an outline or abstract of the proposed manuscript prior to submission of the completed work; please contact the editor for further information.

**Editorials.** Topics in HIV Medicine and its editors invite submission of editorials. Editorials should be approximately 500 to 1500 words (excluding references) and should include numbered references.

**Special Contributions.** A special contribution article often represents the unique contribution (such as a consensus statement) of an author or group of authors and is invited by the editors.

**Stories.** Stories for the “Telling Stories” column share the experiences of those involved in HIV and AIDS care. Stories may be approximately 800 to 3500 words and unsolicited submissions are welcome.

**Letters to the Editor.** Letters to the editor are welcome and should be sent to the address listed below.

**Special Issues.** Topics in HIV Medicine publishes one or two issues each year with a special focus, such as reports from recent scientific meetings and summaries of special International AIDS Society–USA continuing education courses.

**Reprints.** Reprints of papers by expert panels convened by the International AIDS Society–USA are periodically included in Topics in HIV Medicine.

Submission of Manuscripts

Manuscripts should be submitted via e-mail or PC-compatible floppy disk with a double-spaced hard copy to the address below. Each manuscript author should complete an Authorship Form, which is available online at http://www.iasusa.org/pub or may be obtained by contacting the editor at the address below. Outlines or abstracts of proposed manuscripts are welcome and may be sent via mail or e-mail.

Editor, Topics in HIV Medicine
International AIDS Society–USA
1001 B O’Reilly Avenue
San Francisco, CA 94129-1125
E-mail: topics@iasusa.org

Copyright

Copyright to manuscripts published in Topics in HIV Medicine is owned by the International AIDS Society–USA. All authors and contributors of manuscripts accepted for publication, with the exception of US federal government employees, must sign a copyright transfer form as a condition of publication.

Authorship Requirements

Topics in HIV Medicine uses the definition of authorship formulated by the International Committee of Medical Journal Editors and published in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals.1 This definition states: “Authorship credit should be based only on (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Conditions 1, 2, and 3 must all be met. Acquisition of funding, the collection of data, or general supervision of the research group, by themselves, do not justify authorship.”

Financial Disclosure

It is the policy of the International AIDS Society–USA to ensure balance, independence, objectivity, and scientific rigor in all of its educational programs. To that end, all authors and contributors of articles published in Topics in HIV Medicine are expected to disclose to readers any significant financial interest or other relationship with any organization having financial interest in the content of the manuscript. Financial interests include employment, consultancy, honoraria, grant/research support, major stock ownership, and membership in a speakers bureau. The complete financial disclosure statements for all authors and contributors are published with the articles.

---

Topics in HIV Medicine

Subscription Request
Address Change

Topics in HIV Medicine is published 4 to 6 times per year. Please complete this form if you would like to obtain a complimentary subscription or notify the International AIDS Society-USA of a change in address. Subscribers will also receive information about upcoming International AIDS Society-USA continuing medical education courses.

Please mark the appropriate box:

☐ I would like to subscribe to Topics in HIV Medicine. Please send my subscription to the address below.

☐ I am a current subscriber. Please note my change of address below.

IAS–USA ID Number __________ Please see upper left corner of mailing address as shown in sample.

<table>
<thead>
<tr>
<th>First Name</th>
<th>M I</th>
<th>Last Name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Degree or License (MD, RN, PA, none, etc)</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Institution or Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specialty / Primary Field of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Address ( _Home Address _Work Address )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>City</th>
<th>State / Province</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postal Code</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Telephone</th>
<th>Facsimile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>E-mail Address</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

Currently, for how many HIV-infected patients are you providing care? _________

What percentage of your patients are HIV-infected? _______ %

Do you work for a commercial company? Yes [ ] No [ ]

(eg, pharmaceutical, diagnostic, medical product, advertising, insurance, investment, communications)

If yes, please indicate company: ________________________________

Fax or mail this form to: International AIDS Society–USA
1001 B O’Reilly Avenue
San Francisco, CA 94129-1125
Fax: (415) 561-6740

FOR INTERNAL USE ONLY
DATE______________  INITIALS___________  CHANGES ____________________________________________
Educational Programs of the International AIDS Society–USA

Established in 1992, the International AIDS Society–USA is a not-for-profit physician education organization. The mission of the International AIDS Society–USA is to improve the treatment, care, and quality of life of persons with HIV and AIDS through balanced, relevant, innovative, and state-of-the-art education and information for physicians who are actively involved in HIV and AIDS care. The organization’s educational activities are particularly intended to bridge clinical research and patient care.

Collaborative Sessions at Scientific Meetings

IAS–USA Collaborative Interactive Symposium at the 42nd Annual ICAAC
For registered attendees of ICAAC
New Issues and Controversies in the Management of HIV Disease
Saturday, September 28, 2002, 8:30 am–11:00 am
San Diego Convention Center, San Diego, California
Chairs: Douglas D. Richman, MD, and Patrick G. Yeni, MD

IAS–USA/HIVMA Collaborative Interactive Session at the 40th Annual IDSA Meeting
For registered attendees of the IDSA Meeting
Clinical Management of HIV Infections
Saturday, October 26, 2002, 5:30 pm–7:30 pm
Lakeside Center at McCormick Place, Chicago, Illinois
Chairs: Paul A. Volberding, MD, and William G. Powderly, MD

Eighth Annual Fall CME Course Series
Current Challenges in HIV Disease: A Case-Based, Advanced Course in Clinical HIV Management
These courses will present recent advances in clinical HIV management through a mix of didactic lectures and clinically relevant cases developed by a panel of HIV/AIDS experts.

New York, New York
Tuesday, October 15, 2002
Chairs: Douglas T. Dieterich, MD
Roy M. Gulick, MD, MPH
The course will focus on complications of HIV and its therapies.

San Diego, California
Tuesday, November 5, 2002
Chairs: Douglas D. Richman, MD
Wm. Christopher Mathews, M.D., M.S.P.H
The course will include updates from the 2002 ICAAC and IDSA conference.

Cases on the Web
New and updated Cases on the Web presentations are available. Please check www.iasusa.org for details.

Eleventh Annual Winter/Spring CME Course Series
Improving the Management of HIV Disease: Advanced CME Courses in HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management
These courses will review timely and clinically relevant issues in the management of HIV disease, including updates from the 2003 Conference on Retroviruses and Opportunistic Infections.

Los Angeles, California
Saturday, March 8, 2003
Chairs: Ronald T. Mitsuyasu, MD, Paul A. Volberding, MD

New York, New York
Friday, March 28, 2003
Chairs: Gerald H. Friedland, MD, Paul A. Volberding, MD

Washington, DC
Spring 2003
Chairs: Henry Masur, MD, and Michael S. Saag, MD

Atlanta, Georgia
Thursday, March 20, 2003
Chairs: Michael S. Saag, MD, and Jeffrey L. Lennox, MD

Chicago, Illinois
April 2003
Chairs: John P. Phair, MD, and Harold A. Kessler, MD

San Francisco, California
May/June 2003
Chairs: Paul A. Volberding, MD, and Stephen E. Follansbee, MD

Visit www.iasusa.org for agendas and registration forms (generally available 2 to 3 months before each course).

For information about any of these programs, please contact the International AIDS Society–USA.
Phone: (415) 561-6720 • Fax: (415) 561-6740 • E-mail: info@iasusa.org • Web Site: www.iasusa.org
Eighth Annual Fall CME Course Series

Current Challenges in HIV Disease: A Case-Based, Advanced Course in Clinical HIV Management

New York, New York
Tuesday, October 15, 2002

San Diego, California
Tuesday, November 5, 2002

Eleventh Annual Winter/Spring CME Course Series

Visit www.iasusa.org for course agendas and dates.