IN THIS ISSUE

Early Steps in HIV Infection: Targets for Intervention
Discordant Responses to Therapy
Newer Antiretroviral Drugs
HIV in Africa

Reprint:

Also:
New CME Course Schedule
ABOUT THIS ISSUE...

Issue 4 of Improving the Management of HIV Disease summarizes 3 presentations given at the International AIDS Society–USA 1999 winter/spring course series, HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management.

These presentations address a range of different points of intervention in the HIV disease process. At the Boston course in March, Dr Joseph G. Sodroski explained our current understanding of the early stages of HIV infection and the potential of HIV entry into the host cell as a possible target for intervention. At the Chicago course in April, Dr Roy M. Gulick previewed newer drugs and classes of drugs in development for antiretroviral therapy. Also at the Boston course, Dr Amalio Telenti discussed discordant responses to antiretroviral therapy and the clinical implications of such responses.

The fourth article summarizes Dr Susan A. Allen’s presentation on the poor prospects for effective antiretroviral treatment in Africa, given at the International AIDS Society–USA first national course, The Science and Treatment of HIV: An Advanced CME Course for Clinicians, held in March in Snowmass, Colorado. Dr Allen’s article is the first in a 2-part series in IMHD on the status of HIV in Africa. The second article, to be published in the October issue of the publication, will summarize a recent presentation by Dr David A. Katzenstein on the epidemiology of HIV-1 infection in Africa and the divergence of viral subtypes.


Articles in upcoming issues of IMHD will examine immune reconstitution strategies, opportunistic infections in the era of potent antiretroviral therapy, and metabolic complications of antiretroviral therapy.

For information on a new series of International AIDS Society–USA courses and upcoming activities, please see pages 12 and 22–23.

The 1999 national CME course, The Science and Treatment of HIV, was funded solely by the International AIDS Society–USA and did not receive outside commercial support. Unrestricted educational grants supported this issue of Improving the Management of HIV Disease and the 1999 HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management program.

We gratefully acknowledge:

Major, continuous grant support since 1992 from

Bristol-Myers Squibb Company
Glaxo Wellcome Inc.
Roche Laboratories

Substantial grant support from
Abbott Laboratories
DuPont Pharmaceuticals Company
Merck US Human Health

Generous grant support from
Agouron Pharmaceuticals, Inc.
Gilead Sciences
Pharmacia & Upjohn Company
Roxane Laboratories/
Boehringer Ingelheim Inc.
IMPROVING
THE MANAGEMENT
OF HIV DISEASE

A publication of the
International AIDS Society–USA

VOLUME 7 ISSUE 4 SEPTEMBER 1999

EDITORIAL BOARD

Editor in Chief ......... Douglas D. Richman, MD

BOARD OF DIRECTORS

Paul A. Volberding, MD
Professor of Medicine
University of California San Francisco

Constance A. Benson, MD
Professor of Medicine
University of Colorado School of Medicine

Peter C. Cassat, JD
Associate
Dow, Lohnes, & Albertson

Margaret A. Fischl, MD
Professor of Medicine
University of Miami School of Medicine

Harold A. Kessler, MD
Professor of Medicine and
Immunology/Microbiology
Rush Medical College

Douglas D. Richman, MD
Professor of Pathology and Medicine
University of California San Diego and
San Diego Veterans Affairs Medical Center

Michael S. Saag, MD
Professor of Medicine
The University of Alabama at Birmingham

Robert T. Schooley, MD
Professor of Medicine
University of Colorado School of Medicine

Donna M. Jacobsen
Executive Director
International AIDS Society–USA

STAFF AND CONTRIBUTORS

Executive Director .......... Donna M. Jacobsen
Editorial Assistant .......... Amanda Beacom
Manuscript Preparation ........ Matthew Stenger
Copyediting/Proofreading ... Mu'frida Bell, David Sweet
Transcription ............... Steven Akers
Layout/Design ............. Craig High, Diana Voigt
Printing ................... Golden Street Printing

CONTENTS

Presentation Summaries

Early Steps in HIV-1 Infection:
Possible Targets for Intervention .... 4
Joseph G. Sodroski, MD
Mechanisms of HIV-1 Entry into Target Cells...HIV-1
Entry as a Target for Intervention

Discordant Responses to Antiretroviral Therapy .... 8
Amalio Telenti, MD
Possible Mechanisms for the Dissociated CD4+Viremia
Response...Clinical Consequences of Discordant
Responses...Management of Discordant Responses

Antiretroviral Update:
Newer Investigational Drugs .......... 13
Roy M. Gulick, MD, MPH
Emtricitabine (FTC)...Adefovir Dipivoxil...Emivrinine (MKC-442)...Amprenavir...Lopinavir (ABT-378)...Pentafuside (T-20)

HIV Disease and Prospects for Antiretroviral
Therapy in Africa .............. 18
Susan A. Allen, MD, MPH
Happy Delusions...Sad Realities...Competing Demands

Announcements

The Science and Treatment of HIV: An Advanced
CME Course for Clinicians .......... 12

Cases on the Web: An Online CME Activity .......... 22

Activities of the International AIDS
Society–USA .................. 23

Reprint

Use of the Ganciclovir Implant for the Treatment of
Cytomegalovirus Retinitis in the Era of Potent Antiretroviral
Therapy: Recommendations of the International AIDS
Society–USA Panel
Early Steps in HIV-1 Infection: Possible Targets for Intervention

Initial events in the interaction of HIV-1 with target cells and strategies for inhibiting these steps in the infection process were discussed at the Boston course by Joseph G. Sodroski, MD.

Successful entry of HIV-1 into target cells requires membrane fusion mediated by interaction of viral envelope glycoproteins and cell surface receptors. Continued elucidation of the elements of binding and fusion has suggested a number of potential strategies for inhibiting the entry process and thereby preventing productive infection.

MECHANISMS OF HIV-1 ENTRY INTO TARGET CELLS

The exterior of the HIV-1 virion consists of a lipid bilayer membrane in which are embedded trimeric spikes consisting of 3 gp120 molecules surrounding 3 gp41 molecules, with the transmembrane region of the gp41 molecule serving as an anchor in the viral membrane (Figure 1). The interaction between gp120 and gp41 is noncovalent, allowing gp120 to dissociate from the complex under certain conditions. It is currently believed that this event, which inactivates the function of a subset of the viral spikes, allows dissociated gp120 and gp41 to elicit non-neutralizing antibodies, thus serving as an immunologic decoy for the virus. The gp120 glycoprotein has conserved regions and variable (V1-V5) regions that differ among viral strains. The variable regions generally form surface-exposed disulfide-linked loops, whereas the conserved regions are folded into a core composed of an inner domain, an outer domain, and a bridging sheet. The gp41 glycoprotein consists of an exterior domain, the membrane-spanning domain, and an intracytoplasmic tail. The gp120 surface and the exterior domain of gp41 are modified by the addition of N-linked carbohydrates.

Binding and fusion involve the interaction of viral gp120, gp41, CD4 receptors, and secondary receptors on the target cell. The secondary receptors are members of a class of 7-transmembrane G-coupled proteins that serve as chemokine receptors. The 2 primary HIV-1 coreceptors are CCR5 and CXCR4. Primary monocytes and macrophages express CXCR4 and generally not CCR5, whereas primary T-lymphocytes express both receptors (immortalized T-cell lines used to propagate HIV-1 in tissue culture express only CXCR4). During primary and early infection, CCR5-using virus predominates, with a switch to syncytium-inducing virus that utilizes both coreceptors typically occurring over time.

The natural ligands for these chemokine receptors have been shown to inhibit viral entry in vitro by blocking their respective receptors. Natural ligands for CCR5 consist of the β-chemokines RANTES, MIP-1α, and MIP-1β, whereas that for CXCR4 is the α-chemokine stromal cell-derived factor-1 (SDF-1).

Binding of the virion to the target cell is initiated by binding of gp120 to the CD4 receptor; this binding induces conformational changes in gp120 that enable it to bind with high affinity to the coreceptor (Figure 2). X-ray crystallographic studies have enabled the interaction of the viral and cellular components to be visualized. These studies utilized the Fab fragment of a neutralizing antibody that binds to the chemokine-receptor-binding region of gp120, thereby serving as a surrogate chemokine receptor. The gp120-CD4 binding involves a large surface of gp120 spanning the 3 domains of the protein. Figure 3 shows the binding of CD4 in a pocket of gp120, and the 3 domains of the gp120 core; the inner domain interacts with gp41, the outer domain faces outward in the trimeric spike, and the bridging sheet is important for interac-

For a related article on novel targets for antiretroviral therapy, please see the July 1999 issue of Improving the Management of HIV Disease.

Improving the Management of HIV Disease
tion with the chemokine receptor. A feature of the gp120-CD4 interface is an interdomain cavity extending into the interior of gp120 (Figure 4) into which is projected a single phenylalanine 43 (Phe 43) residue of CD4. This component is important for gp120 binding, and the Phe 43 cavity is thus an attractive target for development of drugs for blocking gp120-CD4 binding.

Conformational changes in gp120 upon binding with CD4 allow conserved

regions of the core and the variable region V3 to come into contact with the chemokine receptor on the target cell surface (Figure 4). The V3 loop determines which cellular coreceptor—CCR5 or CXCR4—is to be used. The gp120 region that interacts with chemokine receptors is highly positively charged (i.e., basic), which abets interaction with the highly negatively charged (acidic) N-terminal domain of the chemokine receptor. (It has recently been demonstrated that the CCR5 receptor is more highly negatively charged than initially believed, with charge resulting from both the presence of several acidic amino acids as well as post-translational sulfation of several tyrosine residues.)

Binding of gp120 to the chemokine receptor is believed to induce further conformational changes in the viral envelope glycoproteins that enable the gp41 glycoprotein to mediate virus-cell membrane fusion. Prior to fusion, α helices in the gp41 N-terminus form a coiled-coil structure that initially plays a role in holding the trimer together and in interacting with the gp120 glycoprotein (Figure 5). Binding of gp120 to the chemokine receptor is believed to enable this hydrophobic N-terminus, termed the fusion peptide, to be guided into the cell membrane. The gp41 glycoprotein undergoes a conformational change that results in the interaction of α-C-terminal helices with the N-terminal coiled-coil structure. Since the C-terminal helices are anchored in the viral membrane and the N-terminal helices are embedded in the target cell membrane, this interaction, which may be likened to the springing of a trap, serves to bring the membranes together and permits fusion.

**HIV-1 ENTRY AS A TARGET FOR INTERVENTION**

Based on current knowledge of the binding and entry processes of HIV-1, a number of events could be targeted by antiretroviral drugs, including CD4 binding, chemokine receptor binding, receptor-induced conformational changes, the gp120-gp41 association, and gp41-mediated fusion. A number of drugs have been developed that target some of these processes, including fusion inhibitors, glycosylation inhibitors, soluble CD4, polyanions, and chemokine receptor antagonists.

Peptides that mimic the C-terminal gp41 peptides have been developed and...
Figure 4. Left: gp120 is shown as the large white area, with the location of the CD4 binding site shown in red. Also shown are the variable loops V2, V3, V4, and V5 and the portions of gp120 that interact with the chemokine receptor (dark green areas at bottom of molecule). The blue structures are sugars marking the surface of gp120 that also appear to protect functional portions of the molecule from immune mechanisms. The gp41 glycoprotein attached to gp120 is shown in dark green at mid- to upper left. Right: Projection of the CD4 Phe 43 residue (yellow) into the cavity on gp120. Courtesy of JG Sodroski, MD.

shown to compete for binding of the $\alpha$ helices to the gp41 N-terminal coiled-coil structure, inhibiting the formation of a fusion-competent conformation. The inhibitor pentafuside (T-20), a large 36-residue peptide, has been evaluated in a Phase I/II study in HIV-1 infected patients. In these patients, who received no antiretroviral treatment for several weeks prior to the study, high intravenous doses of pentafuside resulted in a 99% decrease in plasma HIV-1 RNA level. (Please see accompanying Gulick article, Figure 6, page 16) Although there are drawbacks associated with the compound being a peptide and a large molecule, these findings provide proof of principle that targeting conformational changes and the specific interaction between the C-terminal and N-terminal helices of gp41 can block membrane fusion and viral entry and inhibit viral replication in vivo.

The viral envelope glycoproteins are synthesized within the host cell and are extensively glycosylated during the process. Glycosylation inhibitors are directed against the cellular enzymes that modify sugar residues added to the proteins. For the viral glycoproteins gp160, gp120, and gp41, the sugars are initially constructed in elongated form with complex glucose chains at their ends. Under normal conditions, these sugars are trimmed to achieve appropriate length prior to subsequent processing. Inhibition of cellular glucosidases prevents this trimming, leaving the glycoproteins in elongated form. Inhibitors such as deoxynojirimycin and castanospermine block early steps in the final processing of the proteins (Figure 6) and have been shown to effectively block viral infection of new cells in vitro; although viruses produced are still able to bind CD4, they are rendered incompetent for subsequent steps in the entry process. Glycosylation inhibitors acting at later steps (eg, swainsonine) have been less effective at inhibition of infection. The primary drawback of these drugs is that bytargeting cellular enzymes, they also inhibit processing of normal cellular glycoproteins and are thus associated with toxicity.

Soluble CD4 molecules have been used in the attempt to inhibit viral binding to CD4 receptors on target cells by blocking the gp120-CD4 interaction. Although this approach was actively pursued for some time and appeared to be successful with HIV-1 laboratory strains in vitro, enthusiasm for the strategy was dampened by the finding that very high concentrations of soluble CD4 were required to inhibit infection by clinical HIV-1 isolates.

Polyanion compounds bear negative charges that are capable of interfering with the electrostatic interaction of gp120 and chemokine coreceptors, potentially preventing binding with the coreceptors. Most of the polyanion compounds that have been investigated are sulfated compounds. To date, it remains unclear whether the polyanions exhibit sufficient potency or specificity to be effective in a clinical setting, although

Figure 5. Left: Prefusion state of gp41, showing the coiled-coil structure formed by gp41 N-terminal helices (in blue); C-terminal helices are shown in pink, anchored in the viral membrane. The gp120 molecule is directly above the chemokine receptor (on the cell membrane at bottom). Right: The fusion peptide has been inserted in the cell membrane; the C-terminal helices interact with the coiled-coil structure to bring viral and cell membranes into proximity. Courtesy of JG Sodroski, MD.
development of some of these compounds is still being actively pursued.

As noted, the natural ligands for the chemokine receptors used as HIV-1 coreceptors have been found to inhibit infection by blocking receptor binding. AOP-RANTES, a derivative of the natural chemokine, has been shown to inhibit HIV-1 infection in vitro by binding the CCR5 coreceptor without signaling through the receptor, but was inactive in a small clinical trial. Other nonchemokine drugs, including AMD 3100, ALX40-4C, and T-22 (an 18-residue polyphemusin analogue), have been reported to block infection by virus that use the CXCR4 receptor. A small-molecule distamycin analogue has been reported to bind both HIV-1 coreceptors and to inhibit infection by viral isolates irrespective of cellular tropism. A particular challenge in the development of such drugs is to identify molecules that do not inhibit the functions of natural ligands. Although humans with CCR5 gene deletions who do not express the protein appear to be healthy and immunocompetent, it is unclear at present how the inhibition of the more ubiquitous CXCR4 coreceptor might affect health. Gene knock-out studies in mice have indicated that such deletions are associated with adverse effects on hematopoiesis and central nervous system function.

**CONCLUSIONS**

There are a number of conserved features on the assembled envelope glycoprotein complex that appear to be promising as targets for intervention. These glycoproteins, however, have evolved in the in vivo milieu of large-molecule neutralizing antibodies. The heavy glycosylation of the surface of these glycoproteins and the masking of the more conserved regions with variable loops appear to be mechanisms that have evolved to protect functional regions of the glycoproteins from the activity of antibodies directed against the proteins. For therapeutic intervention, attempts will thus be focused on producing small-molecule inhibitors capable of binding to specific regions on the envelope glycoprotein complex or interacting with CD4 or coreceptors. These small-molecule inhibitors should be able to evade the viral defenses designed to block large molecules. It is likely that more of the basic research into the viral entry process will come to fruition in clinical trials over the next several years.

Joseph G. Sodroski, MD, is Professor of Pathology at the Dana-Farber Cancer Institute and Harvard Medical School in Boston, Massachusetts.

**SUGGESTED READING**


Discordant Responses to Antiretroviral Therapy

Responses to potent antiretroviral therapy in the form of increases and stabilization in CD4+ cell count may occur in spite of persistent viremia. Potential biologic explanations and clinical implications of these discordant responses were discussed at the Boston course by Analo Telenti, MD.

Clinicians have been confronted with a diversity of responses to potent antiretroviral therapy. As shown in Figure 1, these responses include not only the optimal suppression of HIV-1 viremia and continuous increase of CD4+ cell count, but also various manifestations of treatment failure. Treatment failure may present with depletion of CD4+ cells following rebound of viremia. However, the diversity of responses also includes a paradoxical failure to reconstitute the immune system despite successful suppression of viremia, and instances of increase and stability of CD4+ cell count in spite of significant viremia. The latter form of discordant response occurs more frequently than the former and may constitute a common response in a substantial number of patients in whom potent antiretroviral therapy is considered to be failing.

Figure 1. Patterns of virologic and immunologic response after initiation of potent antiretroviral therapy. (A) Optimal response, with viral load maintained below assay detection limits and continuous increase in CD4+ cell count. (B) Discordant response of persistent viremia and increase in CD4+ cell count. (C) Discordant response of suppression of viremia and absence of change in CD4+ cell count. (D) Advanced treatment failure. Adapted from Perrin L, Telenti A. Science. 1998;280:1871–1873.

Recent data from the Swiss HIV Cohort Study indicate that antiretroviral therapy produces immunologic and clinical benefit in many patients despite the absence of optimal control of viremia. Laboratory data are providing information on the virologic and immunologic basis for this benefit. Precisely how these combined findings are to influence management of patients with suboptimal control of viremia remains to be determined.

Possible Mechanisms for the Dissociated CD4+/Viremia Response

Reduction in Level of Viremia, Mutations, and Viral Fitness

One potential explanation for the immunologic benefit despite lack of control of viremia is the moderate reduction in viral load observed in patients failing therapy. Explaining this "residual" activity of therapy requires an understanding of changes in the replication kinetics of multidrug-resistant virus. Viral isolates from patients with persistent viremia on potent therapy typically exhibit multiple mutations in the protease and reverse transcriptase (RT) enzymes, and these viruses may exhibit replication defects associated with most of the major primary mutations (Figure 2). In the presence of primary mutations (those appearing early during the development of resistance, and generally involving the active site of the enzyme), the adaptive effort of the virus will include development of secondary mutations that may contribute to improved function of the mutated enzyme. However, secondary, compensatory mutations may not restore full replicative capacity of the virus. Mammano and colleagues have demonstrated, for example, that efficiency of
HIV-1 protease in processing Gag viral protein is decreased in vitro despite compensatory secondary mutations in the enzyme Gag cleavage site, resulting in production of immature virions. Similarly, Back and Berkhout have demonstrated that replicative efficiency is markedly reduced in virus with the RT M184I mutation that precedes the characteristic M184V mutation conferring resistance to the nucleoside reverse transcriptase inhibitor (nRTI) lamivudine. The latter mutation is associated with increased RT function compared with the former, but reduced RT function compared with wild-type virus. (It is noteworthy that this defect is more pronounced in the presence of low intracellular deoxynucleoside triphosphate (dNTP) concentrations, a factor that may explain the observed activity of hydroxyurea in increasing the antiretroviral activity of purine nRTIs in the context of antiretroviral resistance.) Research by Dr Telenti and colleagues indicates that most RT and protease mutations have been associated with measurable changes in viral fitness. Changes in viral infectivity, replicative efficiency, and pathogenicity may affect the relationship of CD4+ cell destruction and production in HIV-1 infection.

### Table 1. CD4+ Cell Recovery in 2 Patients With and Without Multidrug-Resistant HIV

<table>
<thead>
<tr>
<th></th>
<th>Patient 1: Wild-Type HIV-1</th>
<th>Patient 2: Multidrug-Resistant HIV-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CD4+ Count (cells/μL)</td>
<td>69</td>
<td>28</td>
</tr>
<tr>
<td>Current CD4+ Count (cells/μL)</td>
<td>536</td>
<td>424</td>
</tr>
<tr>
<td>Current Viremia (copies HIV-1 RNA/mL)</td>
<td>&lt;100</td>
<td>70,600</td>
</tr>
<tr>
<td>Memory CD4+ (RO+)</td>
<td>56%</td>
<td>26%</td>
</tr>
<tr>
<td>Naive CD4+ (RA+)</td>
<td>41%</td>
<td>59%</td>
</tr>
<tr>
<td>Cells in Cycle (CD4+ Ki67+)</td>
<td>2.1%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

**Altered Cellular Tropism**

An alternative hypothesis for the discordant response is the reduced ability of multiresistant viruses to inhibit T-cell regeneration. Stoddart and colleagues have demonstrated that while both wild-type and resistant viruses are capable of depleting mature CD4+ cells in vivo, they display a different pathogenic potential on thymic precursors. In a SCID-hu mouse (a mouse containing human thymic tissue), only the wild-type virus caused productive infection and depletion of CD4+ cells.

Apart from the decreased damage to thymus implants in animal models, additional evidence from research by Deeks and colleagues demonstrates a prolonged survival of CD4+ cells generated under conditions of persistent viremia under treatment, compared with CD4+ cells in patients with similar degrees of viremia who are not taking a protease inhibitor-containing regimen. In addition, it has been demonstrated that the CD4+ cell count increases observed in patients with multidrug-resistant virus and persistent viremia include increases in CD4+ cells of naive phenotype, irrespective of level of viremia. This finding indicates the potential for immune reconstitution. As illustrated in Table 1, comparison of a patient with controlled viremia and wild-type virus with a patient with significant viremia and multidrug-resistant virus shows comparable percentages of naive CD4+ cells and cells in cycle (Ki67+) in

---

**Figure 2.** Replication kinetics in peripheral blood mononuclear cells of an isolate obtained prior to potent antiretroviral therapy (pre) and a multidrug-resistant isolate obtained from the same patient during therapy (post). Courtesy of A Telenti, MD.
the context of comparable increases in overall CD4+ cell count.

**Other Potential Mechanisms**

Protease inhibitors may induce a sustained CD4+ T-cell response through mechanisms independent of their direct antiviral activity. A recent study by André and colleagues suggests that protease inhibitors may inhibit HIV-specific cytotoxic T-lymphocyte (CTL) activity. In the study, ritonavir, and to a lesser extent saquinavir, reduced major histocompatibility complex-1-restricted antigen presentation in mice infected with the lymphocytic choriomeningitis virus, and thus diminished CTL-mediated antiviral response. No direct effect of aspartyl protease inhibitors on apoptosis pathways (cysteinyl-aspartic proteases) has been shown.

**CLINICAL CONSEQUENCES OF DISCORDANT RESPONSES**

Data from the Swiss HIV Cohort Study indicate a beneficial effect on CD4+ cell counts and clinical progression in patients on potent antiretroviral therapy with persistent viremia. Figure 3 shows changes in CD4+ cell count and plasma HIV-1 RNA level in patients from this cohort who have either (1) maintained plasma HIV-1 RNA level below 400 copies/mL; (2) achieved plasma RNA levels below 400 copies/mL but experienced viral rebound; or (3) never had viremia reduced to below limits of detection (whether as a result of documented resistance or as a result of other factors such as lack of adherence). A 24-month increase in CD4+ cell count of approximately 70/μL occurred in the third group in spite of the relatively small effect on viral load and presumed poor adherence to treatment in an undefined proportion of patients. As shown in Figure 4, data on clinical progression in these groups of patients show degrees of clinical benefit that correspond with the CD4+ cell increases and that are greater for each group than for similar historical comparison groups that were treated prior to the era of potent antiretroviral therapy.

After initiation of potent antiretroviral therapy, a rise in CD4+ cell count by 50/μL or more by 6 months reduced the risk of opportunistic events by 68%.

**Figure 3.** Changes in CD4+ cell count and plasma viremia (mean, 95% confidence interval) according to prior magnitude of control of viremia in patients receiving potent antiretroviral therapy in the Swiss cohort. Courtesy of A Telenti, MD for the Swiss HIV Cohort Study.

**Figure 4.** Rates of progression to death or opportunistic disease according to prior control of viremia in the Swiss cohort compared with rates in patients with similar control of viremia treated in years prior to availability of protease inhibitors and use of potent antiretroviral regimens. Adapted from Ledergerber B. et al. Lancet. 1999;353(9156):863–868.
Discordant Response to Therapy

Achieving a CD4+ cell count of 200/µL during treatment is also associated with a dramatic protective benefit, with a less than 5% risk of an opportunistic event occurring over 18 to 24 months in such patients.

**MANAGEMENT OF DISCORDANT RESPONSES**

How the observation of immunologic and clinical benefit under potent antiretroviral therapy despite persistent viremia impacts clinical management remains unclear (Figure 5). For example, in cases of established virologic failure (as opposed to early treatment failure), should patients with CD4+ cell counts greater than 200/µL with several drug options still available be maintained on the current regimen (perhaps increasing the number of mutations and further improving viral fitness) or should their treatment be altered at the potential expense of losing future treatment options?

Alternately, maintaining a discordant response of sustained CD4+ cell count and persistent viremia may be the sole choice for patients with extensive exposure to antiretrovirals and few remaining treatment options. Switching to a dual-protease inhibitor-containing regimen from a single protease inhibitor-containing regimen in patients with CD4+ cell counts below 200/µL constitutes a treatment option that may produce a protective increase in CD4+ cell count and/or increase of the CD4+ cell count to greater than 200/µL irrespective of whether viremia can be controlled. Data from the Swiss cohort indicate that such a switch in patients with persistent viremia has been associated with additional CD4+ cell count gains of approximately 50/µL. Additional support for maintaining patients with few or no treatment options on potent antiretroviral therapy despite persistent viremia may be provided by the observation of marked increases in viremia and declines in CD4+ cell count when the regimen is withdrawn. Dr Telenti and colleagues have consistently observed such a response to withdrawal of these regimens irrespective of prior degree of control of viremia under treatment (Figure 6).

**CONCLUSIONS**

Discordant responses to potent antiretroviral therapy are not uncommon, particularly the response of increased and then stabilized CD4+ cell count despite persistent viremia. Continuing antiretroviral therapy may represent the only remaining alternative for patients with extensive exposure to antiretrovirals and limited additional options. Such continued treatment may maintain evolutionary pressure on the virus and thus potentially maintain its relatively reduced fitness. In such cases, it is important that adherence to the antiretroviral regimen is maintained, since immunologic progression is characteristic of withdrawal of treatment. When to switch antiretroviral therapy remains a complex issue.

Amalio Telenti, MD, is Chief of the HIV Unit at the University Hospital of Lausanne in Switzerland.

---

**Figure 5.** Proposed algorithm for management of treatment failure. Managing failure requires analysis of 2 factors: whether the failure is early (first record of rebound of viremia) or established, and the number of treatment options available. Courtesy of A Telenti, MD.

**Figure 6.** Effect on CD4+ cell count of interruption of potent antiretroviral therapy in patients with initially controlled viremia and viral rebound, uncontrolled viremia and viral rebound, or uncontrolled viremia and no viral rebound. Adapted from Kaufmann DK, et al. Lancet. 1998;351:723–724.
Suggested Reading


SECOND ANNUAL
THE SCIENCE AND TREATMENT OF HIV
AN ADVANCED CME COURSE FOR CLINICIANS
March 25–March 29, 2000
Snowmass Village, Colorado

Course Chairs
Scott M. Hammer, MD
Michael S. Saag, MD

Course Section Leaders
Judith S. Currier, MD
Daniel R. Kuritzkes, MD
Bruce D. Walker, MD

Course Faculty
Again this year, 15-20 leading scientists and physicians in HIV/AIDS care will speak at this 5-day program.

To receive information on CME credits, agenda, and registration materials, please contact:
International AIDS Society–USA
Presidio of San Francisco
1001 B O'Reilly Ave., PO Box 22916
San Francisco, CA 94129-0916
Symposium Voice Mail: (415) 561-6725
Phone: (415) 561-6720
Fax: (415) 561-6740
E-mail: cme@iasusa.org
Web site: www.iasusa.org

THIS COURSE WILL COVER:

- Basic science issues in development and utilization of antiretroviral treatments
- Complications of HIV/AIDS and antiretroviral therapy
- Treatment strategies and practical problem-solving in patient care
- Future directions in HIV/AIDS management

Participants will hear important up-to-date information from expert faculty in a relaxed, informal setting. Four days of lectures, workshops, and small-group roundtables will allow opportunities for in-depth discussions on complicated issues in HIV management.

Registration fees:
$425 (on or before February 17, 2000)
$525 (after February 17, 2000)

DANIEL F. MARTIN, MD, JAMES P. DUNN, MD, JANET L. DAVIS, MD, JAY S. DUKER, MD, ROBERT E. ENGSTROM, JR, MD, DOROTHY N. FRIEDBERG, MD, PHD, GLENN J. JAFFE, MD, BARUCH D. KUPPERMANN, MD, PHD, MICHAEL A. POLIS, MD, MPH, RICHARD J. WHITLEY, MD, RICHARD A. Wolitz, MD, AND CONSTANCE A. BENSON, MD, FOR THE INTERNATIONAL AIDS SOCIETY–USA

• PURPOSE: To describe the risks, benefits, and recommended use of the ganciclovir implant for the treatment of human immunodeficiency virus–related cytomegalovirus (CMV) retinitis in the era of potent antiretroviral therapy.

• METHODS: A panel of physicians with expertise in the use of the ganciclovir implant and in the management of CMV retinitis was convened by the International AIDS Society–USA. The panel reviewed and discussed available data, and developed recommendations for the use of the ganciclovir implant, the surgical technique, and related management issues. Recommendations were rated according to the strength and quality of the supporting evidence.

• RESULTS: The effect of potent antiretroviral therapy on the immunologic status of patients with human immunodeficiency virus disease has changed the manifestation and course of CMV retinitis in many patients. The clinical management of CMV retinitis and the role of the ganciclovir implant are thus changing. Factors in the decision to choose the ganciclovir implant include the patient's potential for immunologic improvement, location and severity of CMV retinitis, and the risks and costs associated with implantation and concomitant oral ganciclovir therapy.

• CONCLUSIONS: The ganciclovir implant is safe and effective for the treatment of CMV retinitis. The indications for its use should be modified to account for increased patient survival and the potential for CMV retinitis to be controlled by effective antiretroviral therapy. Optimal use of the ganciclovir implant and discontinuation of therapy in selected patients with improvement in immunity may result in better long-term visual outcomes. (Am J Ophthalmol 1999;127: 329–339. © 1999 by Elsevier Science Inc. All rights reserved.)

CYTOMEGALOVIRUS (CMV) RETINITIS IS THE LEADING CAUSE OF VISION LOSS IN PATIENTS WITH ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS). C. Ganciclovir, foscamet, and cidofovir are the most commonly used drugs for the treatment of CMV retinitis. These compounds are initially administered intravenously as induction therapy for 2 to 3 weeks, followed by maintenance...
dosing of either daily intravenous ganciclovir or foscarnet,5 daily oral ganciclovir,6,7 or biweekly intravenous cidofovir.8,9 Whereas each of these drugs is effective for delaying progression of retinitis, disease relapse during maintenance therapy is common and is thought to be inevitable with sufficient follow-up,5,9 particularly if there is no improvement in immune function in response to antiretroviral or immune modulating therapies.

The toxicity profiles and limited efficacy of ganciclovir and foscarnet, as well as the risk of sepsis and the impact on quality of life from the indwelling catheter necessary to deliver long-term intravenous therapy, prompted the development of local drug delivery such as the ganciclovir implant. The ganciclovir implant is a tablet of ganciclovir coated with polyvinyl alcohol, which is permeable to ganciclovir, and partially coated with ethylene vinyl acetate, which is impermeable to ganciclovir.10 This assembly allows slow, continuous diffusion of the drug from the ganciclovir implant into the vitreous cavity that produces higher intracocular levels of ganciclovir (mean, 4.1 μg/ml)11 than can be achieved with maintenance intravenous ganciclovir (mean, 0.93 μg/ml).12–14 This higher sustained level of drug produces a longer therapeutic effect than can be achieved with systemic therapy. In a randomized clinical trial that compared the ganciclovir implant with intravenous ganciclovir, the median time to progression of retinitis in patients treated with the ganciclovir implant was 211 days vs 71 days (P < .001) in patients treated with intravenous ganciclovir.15 However, ganciclovir implant surgery has been associated with complications such as acute and delayed-onset endophthalmitis, retinal detachment, vitreous hemorrhage, malposition of the implant, temporary decreased vision caused by astigmatism, hypotony, and cataract. The ganciclovir implant may be less effective in relapsed CMV retinitis than in previously untreated disease.16 The use of the ganciclovir implant may therefore not be necessary or appropriate in some cases. Finally, the long-term risks of implantation are largely unknown.

Since the ganciclovir implant became widely available in March 1996, potent antiretroviral therapy has become available and recommended for many patients with human immunodeficiency virus (HIV) infection.17,18 A typical treatment regimen for patients with advanced HIV disease includes a combination of three or more drugs, consisting of one or more protease inhibitors and two or more reverse transcriptase inhibitors. This combination of drugs has had a profound impact on the natural course of HIV infection, producing substantial improvement in the function of the immune system and increased survival in many patients.19–23 With this immunologic improvement, there has been a decline in the incidence of opportunistic infections, including CMV retinitis,24,25 and an apparent alteration in the characteristics and course of CMV disease in some patients.26–30 Consequently, some of the fundamental assumptions that have guided the treatment of CMV retinitis have been challenged; anti-CMV therapy may not need to be continued indefinitely, and CMV retinitis is not necessarily a preterminal event. The increased patient survival underscores the need for prolonged and effective control of CMV retinitis if useful vision is to be maintained for life.

The clinical trials that evaluated the ganciclovir implant were conducted at a time when HIV treatment options were limited. It is therefore important to review the role of the ganciclovir implant for the treatment of CMV retinitis in the current era of potent antiretroviral therapy. A panel of physicians with expertise in the treatment of CMV retinitis was convened by the International AIDS Society–USA. The panel reviewed available data and developed current recommendations for the use of the ganciclovir implant. The recommendations herein are rated according to the strength and quality of supporting evidence, by means of a system similar to that developed by the US Public Health Service/Infectious Diseases Society of America31 (Appendix). The recommendations are based on published information whenever possible; in some cases, they are based on the cumulative experience of the members of the panel and are indicated as such. The goal of this report is to assist clinicians in the appropriate use of the ganciclovir implant for the treatment of CMV retinitis and to review information that may affect the management of those patients who elect to receive a ganciclovir implant. These recommendations are intended as general guidelines, and individual circumstances may prompt physicians to modify their treatment strategy.

Indications

NEWLY DIAGNOSED CMV RETINITIS: There are several effective therapeutic options available for patients with newly diagnosed CMV retinitis,4 including the ganciclovir implant11,15,32; systemic therapies (intravenous ganciclovir,5 foscarnet,3 or cidofovir induction8,9 followed by maintenance intravenous therapies or oral ganciclovir regimen9); and intravitreal injections of ganciclovir15,24 foscarin,35 or fomiviren.36 There are certain advantages and disadvantages to each of these management options, and the selection of therapy should be individualized. Factors in this decision include the patient's antiretroviral treatment history and potential for immunologic improvement, current and lowest CD4 T-lymphocyte count, current plasma HIV RNA level, living conditions and lifestyle preferences, and the location of CMV retinitis. CMV retinitis located in zone 1 (within 3000 μm of the fovea or 1500 μm of the disc)37 may prompt a different treatment regimen than that located in zone 2 or 3 (in the peripheral retina) because of the increased risk of vision loss from any progression of retinitis in zone 1. Most of the available treatment options have not been directly compared with the ganciclovir implant. However, a randomized clinical trial comparing the ganciclovir implant plus oral
ganciclovir to intravenous cidofovir therapy for CMV retinitis is currently under way.

The ganciclovir implant offers a number of advantages over systemic therapy, including the longest median time of control of retinitis reported to date.11,15 Better control of retinitis from higher intratocular drug levels may reduce the risk of the emergence of viral resistance. A central line is not required for delivery of drug, which may result in better quality of life; it also eliminates the risks associated with long-term venous access.38,39 The disadvantages include pain and discomfort from surgery, a transient decrease in visual acuity, and the risk of complications inherent in the surgical procedure, which may increase with multiple operations. Because of the lack of systemic anti-CMV effect of the ganciclovir implant, patients remain at risk for developing CMV disease elsewhere.11 Thus, concomitant oral ganciclovir therapy is usually recommended.40

The use of potent antiretroviral therapy (also known as highly active antiretroviral therapy) has created distinct groups of patients based on their potential for immunologic improvement. Indications for use of the ganciclovir implant in these groups may be quite different.

Potent Antiretroviral Therapy–Naïve Patients. For those patients who are motivated to start potent antiretroviral therapy, the goal of anti-CMV therapy should be to stabilize their CMV retinitis while awaiting evidence of immunologic improvement. At present, there are no standard criteria for determining adequate immunologic improvement. A CD4+ T-lymphocyte count of greater than 100 cells per μl, maintained for at least several months, or a rise of at least 50 cells per μl, has been used.26,29,41,42 In addition, it is difficult to predict a patient’s response to antiretroviral therapy and whether the initial response will be maintained, particularly if adverse drug events, poor adherence to therapy, or development of viral resistance to the drugs intervenes. Retinitis may progress in the time it takes for immunologic improvement to develop, thereby increasing the risk of vision loss and retinal detachment. Careful surveillance is recommended. For this group of patients, there are a number of reasonable therapeutic options, as described above. Systemic anti-CMV therapy is generally recommended (A I; see Appendix for classification system) because initial control may be achieved with nonsurgical means and long-term maintenance may not be required. The ganciclovir implant may then be offered if disease relapse occurs. For patients who wish to avoid initial intravenous therapy or have an absolute or relative contraindication to an indwelling catheter or for patients who are intolerant of systemic therapy, the ganciclovir implant is an effective option (A I). It may also be considered in some patients with severe zone 1 disease because of its greater efficacy (B III[1]).

Many patients who present with CMV retinitis and have not previously received potent antiretroviral therapy will have problems with access to care or adherence to a prescribed regimen, and these problems will likely persist after their diagnosis of CMV retinitis. For those individuals in whom immunologic improvement is unlikely because of poor adherence, the ganciclovir implant is an effective treatment option, because control of retinitis does not require active patient adherence (A I).

Potent Antiretroviral Therapy–Experienced Patients. For those individuals taking potent antiretroviral regimens, the development of CMV retinitis is a sign of progressive immune dysfunction, and reassessment of the patient’s antiretroviral therapy is warranted. Numerous options for changing the antiretroviral regimens and the possibility for immunologic improvement may exist for some of these patients, although the probability of substantial improvement may be lower than in antiretroviral-naïve patients. Treatment options for CMV retinitis are similar to those described for potent antiretroviral–naïve patients. Use of the ganciclovir implant in this setting may be the appropriate option for many of these patients, regardless of zone of disease (A III[1]). Observation or options that provide only short-term control of disease are less attractive because of the decreased potential for immunologic improvement.

Patients in Whom Potent Antiretroviral Therapy Has Failed. Given the high penetrance of experience with potent antiretroviral drugs among patients at risk for developing CMV retinitis and the rising incidence of HIV resistance to the drugs, many patients who develop CMV disease may have exhausted their options for meaningful immunologic improvement. The goal of anti-CMV therapy in this setting should be to provide maximum control of retinitis while balancing quality of life issues. The therapeutic options include those described above with the exception of observation. The ganciclovir implant is effective in this setting and may be the preferred treatment for patients with zone 1 disease (A I) and it is an option for patients with zone 2 or 3 disease (A I).

RELAPSED RETINITIS: Relapse of CMV retinitis is a sign of progressive immune dysfunction, and antiretroviral therapy should be reassessed and modified as indicated.17 The most likely reasons for CMV disease relapse other than worsening function of the immune system are inadequate intratocular drug levels12–14 and the development of antiviral resistance.43–45 Once relapse has occurred, intervals between subsequent relapses progressively shorten with continued intravenous therapy.3 Combination intravenous ganciclovir and foscamet is more effective than monotherapy for relapsed CMV retinitis, but the cost and adverse impact on quality of life make this impractical for many patients.46 The ganciclovir implant is usually effective for treatment of relapsed CMV disease47–51 and it should be considered for patients in whom immunologic improvement is unlikely (A II). Previous exposure to
intravenous or oral ganciclovir reduces the probability that the ganciclovir implant will be effective, however. In one study, patients with fewer than 6 months of previous exposure to systemic ganciclovir had a median time to retinitis progression after implantation of 8.0 ± 1.7 months, compared with 2.0 ± 0.3 months in patients with more than 6 months of previous exposure to ganciclovir (P = .016). For patients who relapse after more than 6 months of systemic ganciclovir treatment, there is a greater risk that viral resistance will have emerged, and placement of a ganciclovir implant is less likely to control the retinitis (B II). If the ganciclovir implant alone appears ineffective, the use of intravenous or intravitreal foscan in combination with the ganciclovir implant should be considered (C III[2]). CMV strains with low- and high-level resistance have been isolated. At present, there is no rapid diagnostic test to determine if these mutations are present in the eye. In this setting, a therapeutic trial of intravitreal injections of ganciclovir could be considered before implantation to confirm that the retinitis will respond to higher intracocular levels of ganciclovir (C III[1]), but the dose and frequency of intravitreal injections that would simulate drug levels produced by the ganciclovir implant are unknown. Ganciclovir injections of 2000 μg in 0.05 to 0.1 ml produce intravitreous concentrations of 144 μg per ml at 24 hours, falling to 23 μg per ml at 72 hours. Pharmacokinetics of lower doses of ganciclovir have not been reported, but presumably would better match the 4 μg per ml achievable with the ganciclovir implant.

• BILATERAL DISEASE OR MONOCULAR PATIENTS: The indications for use of the ganciclovir implant in patients with CMV retinitis in both eyes or in the only seeing eye are the same as those described above, and each eye should be considered independently. The risks and costs of surgery would, in effect, be doubled for patients undergoing bilateral ganciclovir implantation. Eyes with immediately sight-threatening retinitis are the best candidates for ganciclovir implant surgery, but eyes with more peripheral disease may respond to oral ganciclovir after induction with intravenous ganciclovir, so that a combination of approaches is possible. Simultaneous surgery should not be performed, but the second eye may undergo surgery as soon as 1 week after surgery in the first eye. A longer interval between surgery allows for more visual recovery in the first eye but prolongs the overall postoperative period. Monocular patients in particular should be aware of the temporary decreased vision that frequently follows surgery (see "Complications" below).

Contraindications

There are few specific contraindications to the use of the ganciclovir implant. For patients with limited life expectancy, the risks (such as the temporary decrease in visual acuity) must be carefully weighed against the potential benefits.

- Patients who have an ongoing ocular surface infection should avoid surgery until the condition is diagnosed and appropriately treated.
- Thrombocytopenia and hemophilia are relative contraindications. However, transfusion with platelets or infusion with factor VIII immediately before surgery has allowed successful placement of a ganciclovir implant in some cases.
- Documentation of ganciclovir-resistant viral strains in the blood or in another organ is a relative contraindication. However, many patients are infected with more than one strain of CMV. Strains present in the blood may not accurately reflect the strain of CMV present in the eye.
- Placement of a ganciclovir implant in patients receiving intravenous cidofovir may be contraindicated. Several panel members have observed profound hyponatremia in eyes treated with this regimen. The pathogenic mechanisms are not known. There is a concern that the breakdown of the blood-ocular barrier associated with surgery may allow higher than usual concentrations of cidofovir into the eye, resulting in ciliary body damage. Alternatively, ciliary body damage associated with previous cidofovir use may be potentiated by surgery. If combination therapy is desired, the panel recommends that intravenous cidofovir not be used for at least 1 month before and after ganciclovir implant surgery (D III[2]).
- The presence of a retinal tear or detachment is a relative immediate contraindication. If a retinal tear is treated with cryopexy or laser, or if a peripheral retinal detachment is treated with laser barricade, a minimum of 2 weeks (or longer if possible) should be allowed to establish good choriretinal adhesion before surgery is contemplated. In addition, the ganciclovir implant procedure may be safely combined with more definitive vitrectom procedures to repair a retinal detachment.

Surgical Technique

The surgical technique to place the ganciclovir implant has previously been described. A number of minor modifications have since been suggested. In general, the following steps are recommended.

1. Prepare the ganciclovir implant before the eye is opened. A backup ganciclovir implant should be readily available should the first implant become damaged or unsterile. The ganciclovir implant occasionally adheres to the packaging. Gently peel the device from the packaging with smooth forceps. It is not necessary to remove small adherent fibers unless they come free easily. In some cases the surface may
FIGURE 1. Ganciclovir implant with hole placed and strut trimmed.

appear irregular, which usually does not indicate a defect in the device.

2. Create a hole in the center of the strut 2 mm from the base with a fine (27- to 30-gauge) needle. Trim the excess strut, leaving no sharp edges (Figure 1). The distance from the hole to the end of the strut should be no more than 0.5 mm. Alternatively, the strut may be trimmed first and then the hole created as described. Pass a double-armed 8-0 nylon suture (on a TG 175 needle) through the hole. Some surgeons tie a knot at the end of the strut to decrease the amount of the strut that is incorporated into the wound. The ganciclovir implant should be kept dry until just before placement in the eye so as to prevent softening of the plastic coating.

3. The ganciclovir implant should be placed in the inferotemporal quadrant between the 6- and 7-o’clock positions for the right eye, and between the 5- and 6-o’clock positions for the left eye. This location, which is more inferior than has previously been specified, maximizes the chance for the ganciclovir implant to exist in an inferior aqueous humor meniscus if the patient subsequently develops a retinal detachment that is repaired with silicone oil, and produces a more desirable cosmetic result because the incision is obscured by the lower eyelid.

4. After opening the conjunctiva, create a 5- to 6-mm pars plana incision 4 mm from and parallel to the limbus by means of an microvitreoretinal or 15-degree blade. A scleral cut-down and cautery of the uvea is generally not necessary. Bleeding may be reduced by creating a full-thickness wound with a single motion.

5. Ensure that the underlying uvea is opened at least three fourths of the length of the scleral incision (briefly gape the wound and inspect) to avoid suprachoroidal placement of the ganciclovir implant.

6. Remove prolapsed vitreous with a vitreous cutter. A complete 3-port vitrectomy is generally not necessary and may lead to a higher rate of complications, including vitreous hemorrhage, retinal detachment, cataract, and hypotony.

7. Grasp the ganciclovir implant strut with heavy nontoothed forceps, orient the sutures so that the needles that will pass through the anterior and posterior lips of the wound are clearly identified, and place the ganciclovir implant into the eye with the drug disk facing anteriorly.

8. Pass the 8-0 nylon suture through the full-thickness sclera of the anterior lip of the wound (from the inside out) with one needle, through the posterior lip with the second needle, and tie with moderate tension only and leave the ends long. This suture is intended to anchor the ganciclovir implant, not necessarily to close the wound.

9. Remove any prolapsed vitreous with the vitreous cutter.

10. Close with 8-0 nylon suture (either a running suture or an X on either side of the anchoring suture) and place the long ends of the anchoring suture under the running or X closure (Figure 2). The closure is designed to avoid any cut suture ends that might protrude from the surface and erode through the conjunctiva. The final knot should be buried in the wound. Additional prolapsed vitreous may need to be removed.

11. Fill the eye with balanced saline solution before final suture tightening, by using either a 30-gauge needle inserted through the pars plana or a cannula inserted through the wound. Tying the knot under normal intraocular pressure may reduce postoperative astigmatism. Close the conjunctiva with an absorbable suture.

12. Verify the position of the ganciclovir implant by direct observation or with the indirect ophthalmoscope at some point after it is placed in the eye.

13. Subconjunctival antibiotics and dexamethasone may be given, followed by cycloplegic drops, an antibiotic ointment, and a light sterile dressing and shield.

Complications

Preoperative counseling should include a discussion of the risks of the procedure, the most common of which are retinal detachment, endophthalmitis, vitreous hemorrhage, cataract, and temporary astigmatism. Additional complications that should be mentioned include hypotony, poor wound healing, cystoid macular edema, and anterior chamber or suprachoroidal placement of the ganciclovir implant. Patients with CMV retinitis are at increased risk for various intraocular complications,
FIGURE 2. (A) Wound closure with an X suture on either side of the anchoring suture. Note that the X suture is started within the wound so that the knot remains buried when the suture ends are trimmed. The long ends of the anchoring suture are placed under the two X sutures. (B and C) Wound closures with a running suture. Note that the suture is started within the wound so that the knot remains buried when the suture ends are trimmed. The long ends of the anchoring suture are placed under the running suture.

independent of treatment modality. For example, cystoid macular edema and epiretinal membranes have been reported after ganciclovir implant surgery, but have also been described as a result of potent antiretroviral therapy–associated immunologic improvement and in patients treated with intravenous cidofovir.61–63 It is therefore important to compare complication rates for adverse events with those associated with systemic therapy as well as those with the natural course of the disease.

• RETINAL DETACHMENT: The 1-year cumulative risk of a retinal detachment in an eye with CMV retinitis treated with intravenous ganciclovir or foscamet ranges from 24% to 50%.64–66 The principal risk factor for developing a retinal detachment is the extent of retinal involvement64–66; activity of disease may also increase the risk.64 The risk of detachment appears to increase linearly with time.66

Placement of the ganciclovir implant may precipitate the development of a posterior vitreous detachment and consequently a retinal detachment. Creation of the large sclerotomy required in ganciclovir implant surgery may result in vitreoretinal traction that may also contribute to the risk of retinal detachment.67 Patients with severe myopia, pseudophakia, extensive lattice degeneration, and previous retinal detachments not related to CMV retinitis may be at increased risk for retinal detachment after intracocular surgery. With increased survival, the long-term risks of sclerotomy-related complications are unknown. However, estimates of the relative risk of retinal detachment in ganciclovir implant–related detachments that result from surgical vs nonsurgical factors are best made by randomized clinical trials. In the first two randomized clinical trials that evaluated the ganciclovir implant, there were several retinal detachments observed between 1 and 2 months postoperatively, with a low risk thereafter during the 8 months of the study.11,15 Neither trial was adequately designed to assess the overall risk for retinal detachment relative to intravenous therapy. It was proposed that there may be an increased risk of early detachment in an eye treated with a ganciclovir implant, but that this risk may be balanced by a decreased long-term risk conferred by the superior control of retinitis that limits the area of retina involved.68 A recent randomized clinical trial confirmed this hypothesis; a small early increased risk for detachment was observed in eyes treated with a ganciclovir implant, whereas in the long term, no statistically significant difference was observed (13% for ganciclovir implant, 17% for intravenous ganciclovir).60

• ENDOPTHALMITIS: Although the reported prevalence of endophthalmitis has ranged from 0.3% to 2.4%,10,40,69 the prevalence in the largest studies conducted to date ranges from 0.3% to 0.5%. Six eyes (0.5%) developed endophthalmitis in a series of 956 eyes in a multicenter study (unpublished data, Bausch & Lomb/Chiron Vision, Irvine, California), and one case (0.3%) occurred in 353 eyes in another multicenter clinical trial.60 The development of endophthalmitis can be a devastating complication, with complete loss of vision in some cases.

• VITREOUS HEMORRHAGE: The incidence of vitreous hemorrhage that affects vision is difficult to ascertain from existing data. In many cases, a small amount of vitreous blood is present in the infero temporal quadrant of the vitreous cavity that usually does not affect vision. When vitreous hemorrhage does affect visual acuity, it is usually transient.11,67 Diffuse mild vitreous hemorrhage was reported in 12 (7.8%) of 154 eyes at 1 week in one study,15 but no significant difference in visual acuity was observed between intravenous ganciclovir–treated eyes and the ganciclovir implant–treated eyes at 4 weeks. Nonclearing vitreous hemorrhage is uncommon but may require vitrectomy to restore vision.

• TRANSIENT DECREASE IN VISUAL ACUITY: There is a temporary decrease in visual acuity in most patients after surgery.11,15 primarily because of postoperative cycloplegia, vitreous hemorrhage, or a temporary astigmatism. Astigmatism averages 0.5 diopter in the axis of the ganciclovir implant incision at 1 week and usually resolves by 4 weeks.
In one study, best-corrected visual acuity was better in eyes in patients treated with intravenous ganciclovir at 2 weeks than in eyes of patients treated with a ganciclovir implant. This difference was not present at 4 weeks or beyond.

- OTHER: Visually significant cataract is an infrequent complication associated with the first ganciclovir implant procedure but may increase with repeated surgical procedures. Small lenticular opacities may occur from lens contact with the ganciclovir implant, but in many circumstances these do not affect vision. In cases in which a cataract is already present when ganciclovir implant surgery is planned, combination surgery can be performed. Conventional phacoemulsification and intraocular lens implantation should be performed first, followed by the ganciclovir implantation as described above (A III[1]). The calculation of intraocular lens power requires modification in eyes with silicone oil.

Fibrovascular proliferation at the pars plana incision site has been demonstrated on histopathologic examination and may be observed at the time of the ganciclovir implant exchange. The long-term risks of this complication are not known, but similar tissue changes after intravitreal injection of vidarabine have caused vitreous traction and retinal detachment. Removal of the ganciclovir implant was adversely affected in one small series, but this problem has not been observed by most members of the panel. Persistent hypotony leading to maculopathy with a transient decrease in vision has been observed on rare occasions.

### Long-term Management

- **CONCOMITANT USE OF ORAL GANCICLOVIR:** The ganciclovir implant should be used in combination with oral ganciclovir if there are no medical contraindications (A I). Concomitant oral ganciclovir (1.5 g three times daily) with the ganciclovir implant reduces the risk of contralateral CMV retinitis and extracapsular CMV disease, prolongs the time to progression of retinitis, and reduces the risk of developing Kaposi sarcoma. The disadvantages of concomitant oral ganciclovir include bone marrow suppression, cost, and the difficulty with adherence to the regimen of nine to 18 pills per day. An oral prodrug of ganciclovir, valganciclovir, is currently in development. The absolute bioavailability of the prodrug is 61% compared with 9% for oral ganciclovir (taken with food), and it can be taken as two tablets once a day, which should improve patient adherence.

- **GANCICLOVIR IMPLANT REPLACEMENT:** The primary reason for CMV disease relapse in an eye treated with a ganciclovir implant as the initial form of CMV therapy is the depletion of drug from the device. Treatment with a second ganciclovir implant results in continued control of disease in most patients. Whether preemptive replacement of the ganciclovir implant will decrease the risk of these reactivations is a complicated question, and no clinical trial has been adequately designed to answer it. In one study, routine ganciclovir implant exchange was performed at 32 weeks and produced a good clinical result, with 75% of eyes being free of progression until the patient died. A fundamental assumption during this trial was that retinitis would reactivate when drug delivery ceased because immune function would continue to decline. Since the widespread implementation of potent combination antiretroviral therapy, the characteristics and course of CMV retinitis have been altered in some of these patients. In addition, concomitant use of oral ganciclovir extends the median time to progression of retinitis in eyes treated with a ganciclovir implant to beyond 1 year. For these reasons, planned replacement of the ganciclovir implant at fixed intervals is not recommended for most patients at this time (D III[1]). A possible exception involves patients who have exhausted all options for immunologic improvement and have zone 1 CMV retinitis, such that reactivation may lead to rapid and irreversible vision loss. In this setting, preemptive replacement of the ganciclovir implant should be considered (A III[1]). For patients with CMV retinitis in zone 2 or zone 3 who have exhausted all antiretroviral options and remain profoundly immunocompromised, preemptive ganciclovir implant replacement may be considered (B III[1]). For those patients who do not receive a replacement ganciclovir implant, monthly follow-up is recommended so that relapse of disease can be promptly identified and treated. The routine removal of the original ganciclovir implant is not necessary in patients who experience immunologic improvement and do not require a subsequent ganciclovir implant (D III[1]).

Although the published data concerning ganciclovir implant replacement are much less extensive than those for primary placement, the surgical risks appear greater with multiple procedures. In particular, vitreous hemorrhage, cataract, and hypotony appear more common. Placement of an infusion line is not usually necessary when an implant is placed in a patient with multiple previous implant surgeries, but it can be considered if intraoperative hypotony is profound. Patients who require multiple implant procedures (indicating persistent immunocompromise) are often sicker than patients undergoing primary implant surgery, which may increase the risk of complications.

The options for placement of another ganciclovir implant include (1) the removal of the original ganciclovir implant and placement of another ganciclovir implant through the same wound (same-site technique or exchange) or (2) the placement through another, noncontiguous site, most commonly the inferonasal quadrant (separate-site technique). Placement through a wound contiguous with the original has been described but is not commonly used. The advantages of the same-site
technique are that the amount of permanent hardware in the eye is minimized, and less surface area of the sclera is disturbed, resulting in a better cosmetic result. If a same-site technique is employed, it may be prudent to use the site no more than twice, although third and fourth operations using the same wound have been successfully performed. The advantages of a separate-site technique include the potential to avoid some of the complications that have been reported with a same-site technique. These potential complications include an increased risk of vitreous hemorrhage from entry through a vascularized wound, separation of the drug disk from the strut at the time of ganciclovir implant removal,77,78 and poor wound healing from multiple entries through the wound. No large series of second ganciclovir implant procedures using a separate-site technique has been reported, and therefore a comparison of complication rates is not possible. Either technique is acceptable, with the decision being driven primarily by surgeon preference. If a separate-site technique is used, the original ganciclovir implant is not usually removed.

- SILICONE OIL: Anecdotal experience suggests that the ganciclovir implant is capable of releasing drug in eyes filled with silicone oil. Ganciclovir is a water-soluble compound and would not be expected to partition into oil. In most retinal reattachment procedures, only 80% to 90% of the vitreous cavity is filled with oil and an inferior meniscus of aqueous humor remains. If the ganciclovir implant is placed in an inferior location, it may exist in this meniscus and release drug. Exchange of the ganciclovir implant in an eye with silicone oil may result in loss of oil that may need to be reinflused.

However, use of the ganciclovir implant is sufficiently cost-effective compared with intravenous therapy that Medicare, Medicaid, and private insurance companies will pay for the procedure.

---

**Conclusions**

THE AVAILABILITY AND USE OF POTENT ANTIRETROVIRAL therapy has produced an increase in survival of patients with HIV disease and AIDS, as well as a decrease in the incidence and a modulation of the course of many opportunistic infections that complicate the syndrome. Use of the ganciclovir implant has resulted in better control of CMV retinitis and improved quality of life for many patients with HIV-related CMV retinitis, but physicians and patients should be aware of the potential complications associated with surgery. Its appropriate use in the era of potent antiretroviral therapy will require continued attention to the epidemiology and manifestations of both CMV retinitis and HIV infection as experience with these therapies continues to evolve and newer drugs become available.

---

**APPENDIX. Levels of Strength and Quality of Evidence Used for Recommendations**

<table>
<thead>
<tr>
<th>Categories of the strength of the evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Strong evidence of efficacy and substantial clinical benefit</td>
<td>Support recommendation for use; should always be offered.</td>
</tr>
<tr>
<td>B. Moderate evidence of efficacy or strong evidence of efficacy, but only limited clinical benefit</td>
<td>Supports recommendation for use; should generally be offered.</td>
</tr>
<tr>
<td>C. Evidence of efficacy is insufficient to support a recommendation for or against use or evidence of efficacy may not outweigh adverse consequences</td>
<td>Should never be offered.</td>
</tr>
<tr>
<td>D. Moderate evidence of lack of efficacy or adverse outcome supports a recommendation against use</td>
<td></td>
</tr>
<tr>
<td>E. Good evidence of lack of efficacy or adverse outcome</td>
<td></td>
</tr>
</tbody>
</table>

Categories reflecting quality of evidence

I. Evidence from at least 1 properly randomized controlled trial

II. Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled experiments

III. Opinions of the panel

[1] Unanimous agreement among the panel

[2] General but not unanimous agreement among the panel

*Adapted from Gross and associates.34*
ACkNOWLEDGMENT

Joshua S. Babcock and Misako E. Hill of the International AIDS Society–USA provided administrative assistance in organizing the panel of experts.

References


33. Cocheure-Massin I, LeHoang P, Lautier-Frau M, et al. Efficacy and tolerance of intravitreal ganciclovir in cytomegalo-


338 AMERICAN JOURNAL OF OPHTHALMOLOGY MARCH 1999


Authors Interactive®
We encourage questions and comments regarding this article via the Internet on Authors Interactive® at http://www.ajo.com/ Questions, comments, and author responses are posted.
ANTIRETROVIRAL UPDATE: NEWER INVESTIGATIONAL DRUGS

Characteristics of selected new drugs from established and novel classes of antiretrovirals were discussed at the Chicago course by Roy M. Gulick, MD, MPH.

As of mid-1999, 14 antiretroviral drugs have been approved for use in treating HIV-1 infection. A large number of newer, investigational drugs representing established and novel classes are at varying stages of development (Table 1). Some of these drugs may prove to provide partial remedies to limitations of current regimen options, including problems with adverse effects and tolerability, pharmacokinetic interactions, adherence, and resistance and cross-resistance. Dr Gulick described the characteristics of selected investigational drugs from each antiretroviral class: the nucleoside reverse transcriptase inhibitor (nRTI) emtricitabine, the nucleotide reverse transcriptase inhibitor (nRTI) adefovir, the nonnucleoside reverse transcriptase inhibitor (NNRTI) emivirine, the protease inhibitors amprenavir (recently approved) and lopinavir, and the fusion inhibitor pantasufide.

**Figure 1.** Median change in plasma HIV-1 RNA level during adefovir monotherapy. Adapted from Deeks SG, et al. J Infect Dis. 1997;176:1517–1523.

**EMTRICITABINE (FTC)**

The nRTI emtricitabine (FTC) exhibits anti-HIV-1 potency in vitro 4 to 10 times greater than the related drug lamivudine and also exhibits activity against hepatitis B virus. The proposed dosage of the drug is 200 mg once a day; didanosine is the only currently-approved nRTI routinely given on a once-daily schedule. Phase III studies of emtricitabine are under way. Adverse effects have been uncommon, consisting primarily of gastrointestinal tract effects and headache. The drug is eliminated largely via renal mechanisms. Resistance in vitro is conferred by the reverse transcriptase M184V mutation associated with lamivudine resistance, indicating cross-resistance between the 2 drugs. In a Phase I dose-escalation study of emtricitabine, 200 mg once a day or twice a day exhibited a trend toward greater reduction of serum viral load, achieving maximal reductions of greater than 1.5 log. Data from a subsequent Phase II/III study indicate similar degrees of effect of once-daily dosing of 25, 100, or 200 mg emtricitabine and 150 mg twice a day of lamivudine.

**ADEFOVIR DIPIVOXIL**

The nRTI adefovir dipivoxil is in Phase III studies and studies in antiretroviral-experienced patients and currently is available through an expanded access program. Adefovir exhibits in vitro potency against HIV-1 (90% effective dose [ED90] of 0.007-7 mM), as well as against cytomegalovirus and hepatitis B virus. The proposed dosage is 60 mg once a day; there are no food restrictions with usage. The drug undergoes renal excretion. Adverse effects include gastrointestinal tract effects, fatigue, and proximal renal tubular dysfunction. In vitro resistance mutations have been detected at reverse transcriptase codons 70, 69, and 65. The emergence of mutations in vivo has been uncommon to date. Figure 1 shows degree of reduction in viral load in a Phase I study with an initial formulation equivalent to the current 120 mg dose. In a virologic substudy of a Phase II study in which adefovir was added to existing regimens, it was observed that a greater decrease in plasma HIV-1 RNA level (0.94 log) occurred in patients exhibiting the M184V lamivudine-associated resistance mutation than
patients, decreases in viral load were comparable in the 2 groups, and a reduced incidence of increases in serum creatinine of at least 0.5 mg/dL over 42 weeks was reported with the 60 mg dose (Figure 2). Given its apparent absence of cross-resistance with other drugs but relatively modest virologic effect and the concern over toxicity, adefovir may be best suited for use by antiretroviral-experienced patients with limited therapeutic options. It currently is being evaluated in a large number of studies of patients in whom protease inhibitors have failed.

EMIVIRINE (MKC-442)

The NNRTI emivirine (MKC-442), a uracil analogue that has the chemical structure of a nucleoside, is highly potent against HIV-1 in vitro (90% inhibitory concentration [IC₅₀] of 10-98 nM). The proposed dosage is 750 mg twice a day (no food restrictions), and the drug is metabolized primarily by the cytochrome P450 3A4/5 isozyme system and partially by the cytochrome P450 1A2 system. Penetration of the drug into the central nervous system has been observed in animal studies. The drug currently is in Phase II/III evaluation. Adverse effects have included nausea, headache, dizziness, diarrhea, and rash, the latter of which has been observed in approximately 10% of patients. Figure 3 shows the effect of emivirine monotherapy on viral load in a dose-escalation study, indicating a decrease of approximately 1.5 log with the 750 mg twice-daily dosage. Genotypic analysis has indicated that resistance to emivirine is in some patients associated with mutation at reverse transcriptase K103N, suggesting the likelihood of cross-resistance with other NNRTIs. Patients taking MKC-442 who do not develop the K103N mutation, however, retain susceptibility to other NNRTIs. The optimal sequencing of NNRTIs requires further study.

AMPRENAVIR

The protease inhibitor amprenavir was recently approved for use at a dose of 1200 mg (eight 150 mg capsules) twice a day. It is the first approved protease inhibitor that does not require food restrictions. The drug is metabolized via the cytochrome P450 3A4 isozyme system, and like indinavir and nelfinavir, it is a cytochrome P450 3A4 inducer. The most common adverse effects of amprenavir are rash and gastrointestinal tract effects. Mutations associated with resistance in vitro occur at the protease codons 50, 46, and 47, mutations that have generally not been described for other protease inhibitors; resistance mutations have also been detected at gag cleavage sites and described in the clinical setting.

Amprenavir is potent in vivo as a single drug, resulting in initial reductions in viral load of approximately 1.5 log; as with other single drugs, viral breakthrough occurs fairly rapidly after
Resistance mutations associated with lopinavir in vitro have not included the characteristic protease codon 82 mutation

initiation of treatment (Figure 4). The AIDS Clinical Trials Group (ACTG) 347 study compared amprenavir alone with amprenavir/zidovudine/lamivudine. The amprenavir monotherapy arm was discontinued early due to viral breakthrough. A subset of patients from this arm has been enrolled in ACTG 373, which is evaluating the effects of a subsequent regimen of indinavir/nevirapine/stavudine/lamivudine. Preliminary results of this study show good antiviral activity of the regimen, suggesting at least the potential for replacement of failing amprenavir-containing regimens with indinavir-containing regimens.

A small open-label evaluation of the combination of amprenavir and the nRTI abacavir has suggested a durable effect on viral load of this double combination. Approximately 90% of patients exhibited reduction in plasma HIV-1 RNA to below 500 copies/mL, with approximately 80% exhibiting reductions to less than 50 copies/mL over the course of extended follow-up. These findings suggest that additional investigation of double combinations of potent drugs may be warranted.

ACTG 398 is a large study that should provide guidance on the potential role of amprenavir in regimens for patients in whom initial protease inhibitor therapy has failed. In this study 481 patients with more than 4 months of treatment with up to 3 protease inhibitors and plasma HIV-1 RNA levels of at least 1000 copies/mL are being treated with a regimen of amprenavir/abacavir/efavirenz/adevirov plus either saquinavir soft-gel capsule, indinavir, nelfinavir, or matching placebo. Treatment is to continue for at least 72 weeks. Results are expected to provide some idea of the potential of such regimens to exert antiretroviral activity in the context of prior protease inhibitor failure.

Findings suggest additional investigation of double combinations of potent drugs may be warranted

LOPINAVIR (ABT-378)

The protease inhibitor lopinavir (ABT-378) is a potent inhibitor of HIV-1 in vitro (IC\textsubscript{50} of 0.07 μM). The proposed dose of the drug is 400 mg twice a day to be administered with ritonavir 100 mg twice a day; like saquinavir, lopinavir levels are markedly increased in the presence of small concentrations of ritonavir due to their pharmacokinetic interaction. The drug will be formulated as capsules containing 133 mg of lopinavir and 33 mg of ritonavir, and should be taken with food. As with other protease inhibitors, the drug is metabolized by the cytochrome P450 3A4 isoenzyme system. Lopinavir currently is being evaluated in Phase III studies and studies in antiretroviral-experienced patients. The most common adverse effects have been abnormal stool consistency and diarrhea. The drug was designed with the aim of avoiding the characteristic protease inhibitor-associated resistance mutation at protease codon 82; resistance mutations in vitro have occurred first at codon 84 and then at other sites, as well as at gag cleavage sites. Figure 3 shows virologic response in a study of lopinavir/ritonavir
twice a day plus stavudine and lamivudine. Suppression of viral load has been maintained over 6 to 9 months, with more than 90% of patients achieving HIV-1 RNA levels of less than 400 copies/mL.

An ongoing trial is evaluating the effects of lopinavir in 70 protease inhibitor-experienced patients. Patients have more than 12 weeks of protease inhibitor treatment and are nRTI-naive and have plasma HIV-1 RNA levels of 1000 to 100,000 copies/mL. Patients are receiving lopinavir/ritonavir 400 mg/100 or 200 mg twice a day, nevirapine, and a new nRTI. Recently reported results show that 84% of patients reduced their viral load levels to below 500 copies/mL at 24 weeks in an on-treatment analysis. Further follow-up results are forthcoming.

PENTAFUSIDE (T-20)

Pentafuside (T-20) is a viral fusion inhibitor that blocks interaction of the viral envelope gp41 with the target cell membrane during the fusion process. (Please see accompanying article, page 4). The drug exhibits an IC₅₀ of 1.7 ng/mL against HIV-1 in vitro. The proposed dosage of pentafuside currently is uncertain, although as a peptide the drug requires intravenous or subcutaneous administration. Dose-escalation studies indicate a potent virologic effect at intravenous doses of 100 mg twice a day; subsequent study of continuous infusion and subcutaneous administration indicate a superior effect with subcutaneous administration of 100 mg twice a day (Figure 6). The route of metabolism of pentafuside currently is unclear, and adverse effects have not been well characterized, with some patients in early studies reporting fever or headache. Pentafuside-associated resistance mutations in the viral gp41 have been observed both in vitro and in vivo, accounting for the rebound of viral load levels over a few weeks when the drug is used singly.

A second fusion inhibitor, T-1249, is in early clinical development. This peptide compound appears to demonstrate activity in vitro against pentafuside-resistant virus.

CONCLUSIONS

Much progress has been made in the treatment of HIV infection over the last few years by the development and widespread use of potent antiretroviral regimens. However, current regimens are limited by inconvenience, adverse effects, and resistance and cross-resistance. Newer drugs in development include new members of existing classes of drugs (nRTIs, NNRTIs, protease inhibitors) and new classes of drugs (nRTIs, fusion inhibitors). These newer drugs include those that can be dosed once or twice daily, with different adverse effect profiles and, in some cases, with demonstrated activity against resistant virus. Further progress in the field will stem from continued research and development of newer antiretroviral drugs.

Figure 5. Proportion of patients receiving lopinavir/ritonavir twice a day plus stavudine and lamivudine with plasma HIV-1 RNA level less than 400 copies/mL. Courtesy of SC Brun, MD, Abbott Laboratories, Abbott Park, IL.

Figure 6. Left: Mean change in plasma HIV-1 RNA according to pentafuside intravenous dosage. Adapted from Kilby JM, et al. Nat Med 1998;4(11):1302–1307. Right: Median change in viral load according to continuous infusion (CSI) dosage or subcutaneous twice-daily dosing. Courtesy of J Lalezari, MD, San Francisco, CA.
SUGGESTED READING


HIV Disease and Prospects for Antiretroviral Therapy in Africa

The small prospect for extending effective antiretroviral treatment to the HIV-infected populations of African nations and the political, social, and economic factors contributing to this disastrous situation were discussed at the International AIDS Society–USA national CME course by Susan A. Allen, MD, MPH. Her presentation was divided into discussion of “happy delusions,” “sad realities,” and “competing demands.”

HAPPY DELUSIONS

A number of “happy delusions” regarding the ability to institute effective programs for antiretroviral treatment of HIV-infected individuals in Africa continue to be harbored even by those with first-hand experience of the daunting obstacles to such an endeavor. Among these delusions are the beliefs that (1) antiretroviral drugs will be inexpensive enough for use by these populations in the foreseeable future; (2) efficient distribution systems will be established; (3) adherence will be better than it has been for other diseases; and (4) governments and donors will prioritize HIV disease over other major causes of death. Short rejoinders to these hopes include the facts that in Africa, which currently hosts more than 80% of the world’s HIV infections, average annual income is approximately US $100; attempts to set up efficient distribution systems for other widespread life-threatening diseases that are more easily treated have had limited success; adherence to simpler regimens than that required for HIV disease treatment has been poor; and there are major health problems that are more urgent or that can be addressed more cost-effectively than HIV disease. However, a fuller appreciation of the magnitude of the barriers confronting effective treatment programs requires appreciation of current environmental and socioeconomic aspects of life in much of Africa.

SAD REALITIES

Factors contributing to the unlikelihood of extending effective anti-HIV treatment to the broad population of infected individuals include (1) regional and national political instability; (2) a combination of growing populations and shrinking resources; (3) existence of other endemic health problems (including childhood diseases, malaria, other sexually transmitted diseases, and tuberculosis); and (4) inefficiency, corruption (5) and apathy at international, national, and local organizational and governmental levels.

Difficulties in establishing effective treatment programs are illustrated by the status of tuberculosis treatment efforts in Africa. Sub-Saharan Africa has among the highest incidence rates of tuberculosis in the world. Although curative drug therapy exists and is relatively inexpensive (approximately US $100 per clinically active case), and despite the existence of both an international donor agency that provides drugs to developing country governments and national programs to diagnose tuberculosis and distribute the drugs, the disease remains woefully undertreated. In part, this is due to infrastructure limitations. Trained personnel and electricity required for diagnostic microscopy and chest x-rays are often lacking, as are funds for x-ray film. Drug distribution systems often are weak, primarily as a result of theft of drugs at every point in the distribution system.

Financial incentives also lead to the common practice of patients taking several weeks of medication until they feel

![Figure 1. HIV-positivity rates among 12,000 cohabiting heterosexual couples in Lusaka, Zambia. Adapted from McKenna SL, et al. AIDS. 1997;11(suppl 1):S103–110.](image-url)
better and selling the remainder of their supply. Even with directly observed therapy (DOT), which is associated with the expense of additional personnel or labor-hours, patients have been known to hold pills under their tongue until they leave the clinic; “wet” pills have a slightly lower street price than “dry” pills. In addition to these infrastructure problems, biologic factors have increased the difficulty of successful treatment, including the HIV-related increase in number of tuberculosis cases, the greater difficulty in diagnosis of HIV-related cases, and the emergence of drug-resistant bacterial strains.

The inability to maintain effective programs for a 6-month treatment course for tuberculosis does not bode well for success of maintaining programs for the extended treatment required for HIV disease. Prospects may be better, however, for programs for short-course treatment to prevent perinatal transmission. Programs for screening and treatment of syphilis in the prenatal care setting, which may serve as a model for perinatal transmission prevention efforts, have generally been successful as a result of the soundness of the infrastructure for prenatal care in most locales. In most of Africa, standard of care in prenatal care programs includes screening for and treatment of syphilis. Current rapid plasma reagin (RPR) positivity prevalence rates in these settings are 5% to 20%. Diagnosis, accomplished with the RPR card, is inexpensive (approximately US $0.20) and does not require electricity or specialized personnel. Curative treatment, achieved with a single dose of penicillin, is also inexpensive (a few cents), and all commodities are supplied by an international donor agency. However, even in this setting, success has not been overwhelming, as a result of reluctance of nursing staff to draw blood and perform card tests and of problems with stocking and distribution of reagents resulting from theft.

Assuming effective treatment programs were feasible, it is rational to believe that efforts to widely implement HIV testing and counseling in order to prevent transmission might be undertaken or maintained. Initial studies by Dr. Allen and colleagues conducted in Rwanda showed that testing and counseling were effective in preventing heterosexual transmission of HIV. Currently, Dr. Allen and colleagues are testing and counseling cohabiting heterosexual couples in Lusaka, Zambia. Heterosexual couples constitute 90% of the adult population of urban areas in Zambia. Lusaka has a population of approximately 2 million, with testing in prenatal care clinics indicating a HIV seropositivity rate of 25% to 30%. Community workers publicize the program and approximately 20 couples at a time are brought to the testing center, where 2 HIV tests are performed. Lunch is provided while results are obtained; after being informed of test results and receiving counseling, the couples are provided with bus fare home. Approximately 12,000 couples have undergone testing, with results showing 57% of the couples with 2 HIV-seronegative partners, 23% with 2 HIV-seropositive partners, and 20% discordant for infection, with equivalent proportions of male and female partners in the discordant couples testing HIV-positive (Figure 1).

The mean duration of union for these couples is approximately 5 years and greater than 97% have children together. Testing and counseling, including provision of condoms, have reduced HIV acquisition/transmission rates among discordant-seronegative couples from approximately 3% to approximately 0.5% per year and transmission rates in discordant couples from 20% to 25% to less than 10% per year. The effectiveness of such a program has recently been confirmed in a 3-country randomized, controlled trial conducted by Coutes and
colleagues. With the use of rapid testing (at a cost of less than US $1 per kit), the cost of prevention of 1 case of HIV infection via a program targeting couples is calculated to be US $75 (compared with an approximately 3-fold greater cost for short-course antiretroviral treatment to prevent 1 case of maternal-child transmission).

Although international and bilateral agencies endorse the concept of such programs, they are unwilling to provide funding, and many local governments currently are cutting programs because of lack of resources. The primary reasons for reluctance among potential donors appear to be the desire to avoid programs that involve recurring costs (eg, salaries) and commodities, and the desire to avoid the responsibility attendant upon identification of HIV-infected persons. Donor agencies and governments are fearful of backlash from the HIV-seropositive constituency and activist groups likely to form once knowledge of infection status is widespread. Further, many think that it is too late for anything to be done for the adult population, and that prevention efforts should focus on youth.

With all of this in mind, it appears that the best solution for preventing further spread of HIV infection and a disastrous impact on subsequent generations is an HIV vaccine. Vaccination programs have had a high degree of success in developing nations. The vaccine would be inexpensive and could be given without HIV testing or counseling. In addition, it could be integrated into existing prenatal and childhood vaccination programs.

COMPETING DEMANDS

A number of factors have conspired to keep the HIV epidemic at a lower priority for many African nations, including the high number of natural disasters affecting the continent. Statistics for 1988 to 1992, for example, show that there were 66 events that caused damage amounting to more than 1% of a nation’s gross national product and 139 events that affected more than 1% of the population. The costs of natural disasters alone in Africa have averaged US $87 billion per year over the past 25 years; by comparison, international donor agencies provide approximately US $3 billion per year to African nations.

War and its consequences constitute another major factor in the relegation of HIV disease to lower priority (Figure 2). Many of the sub-Saharan African nations are currently embroiled in conflicts, including the current conflict in Congo that threatens to involve multiple surrounding nations, or are in transitional postconflict states. The 1994 genocide campaign in Rwanda claimed 1 million lives in the course of 4 months (ie, more lives than HIV disease is likely to claim in decades) and created an enormous refugee population, with 2 million people crossing Rwanda’s borders within several weeks. As related by Dr Allen, who was working in Rwanda during this period, concerns over a disease that may claim a life at some unspecified time in the future pale against the immediacy of such a disaster.

In addition to direct casualties of war, such large movements of people are associated with sharp increases in mortality due to disease (eg, cholera, meningitis). Mortality does not attend only refugee movements, but is also dramatically increased among internally displaced persons. Figure 3 shows the magnitude of such increases during recent upheavals in Somalia and Sudan. These occurrences also have a disastrous impact on social and health care infrastructures. A recent assessment of 171 developing countries in achieving international development goals defined by a combination of health and demographic factors shows that African nations account for 25 of the 34 nations furthest away from these goals, with the majority of these nations currently or recently in-

![Figure 3. Increases in crude monthly mortality rates among internally displaced persons (IDP) during conflicts in Somalia and Sudan in early 1990s. CMR indicates deaths per 1000 per month. Adapted from the World Health Organization, http://www.who.int/eha/emergenc/soe.](image-url)
volved in political conflicts.

These competing demands for resources and the more immediate threats to life reinforce the unlikelihood that antiretroviral treatment will become a reality for the majority of infected individuals in African nations. Although the expense of treatment may decrease markedly in the foreseeable future, the fact that the political and economic status is worsening instead of improving in most countries suggests that treatment will remain out of reach for most. Limited use is likely among some populations in nations with relatively healthy economies (eg, South Africa), but overall, less than 1% of the African population can currently afford to pay for treatment on their own or work for companies willing to pay for it. Some nations that have been involved in conflicts have few individuals remaining who are capable of running a government; in such places, governments are setting aside funds for treatment of infected officials to prolong their life as long as possible. For the remainder of the HIV-infected population, there are no obvious or apparent solutions.

Susan A. Allen, MD, MPH, is Associate Professor of Epidemiology at The University of Alabama at Birmingham.

SUGGESTED READING


Cases on the Web

An ongoing series of case-based, advanced online CME activities from the International AIDS Society-USA on HIV InSite

CASE TOPICS

Available from August 1, 1999 to October 31, 1999
Clinical Management Issues in Antiretroviral-Experienced Patients
by Paul A. Volberding, MD
University of California San Francisco

Coming soon
Metabolic Complications of Antiretroviral Therapy
by Frank J. Palella, MD
Northwestern University School of Medicine

The Potential Use of Resistance Testing in Antiretroviral Management
by Michael S. Saag, MD

EDITORS

Editor in Chief
Michael S. Saag, MD, Professor of Medicine
Director, AIDS Outpatient Clinic, The University of Alabama at Birmingham

Co-Editor
Meg Newman, MD, Assistant Professor of Medicine
University of California San Francisco

CME ACCREDITATION

Cases on the Web is sponsored by the International AIDS Society-USA.

This program has been planned and produced by the International AIDS Society-USA in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME).

The International AIDS Society-USA is accredited by the ACCME to sponsor continuing medical education for physicians.

The International AIDS Society-USA designates these educational activities for a specified number of hours in category I credit toward the AMA Physician's Recognition Award (the number of hours will be noted with each activity). Each physician should claim only those hours of credit that he/she actually spent in the educational activity.
ACTIVITIES OF THE INTERNATIONAL AIDS SOCIETY–USA

BRIDGING CLINICAL RESEARCH AND PATIENT CARE THROUGH QUALITY EDUCATION FOR PHYSICIANS

IDSA INTERACTIVE SESSION

International AIDS Society–USA Interactive Session at the IDSA 37th Annual Meeting: Antiretroviral Therapy Decision Making in the Combination Therapy Era

Philadelphia, Pennsylvania, Saturday, November 20, 1999
5:15 PM to 7:15 PM

Chairs: Constance A. Benson, MD, and Paul A. Volberding, MD
Faculty: Judith A. Aberg, MD, Scott M. Hammer, MD, Victoria A. Johnson, MD, Michael S. Saag, MD, and Robert T. Schooley, MD

Co-sponsored by the IAS–USA and the IDSA. Topics will include initial therapy, opportunistic infection prophylaxis, current complications of HIV, strategies for antiretroviral failure, and resistance testing. Expert faculty will use clinical decision points as a springboard for discussion of new data. Open to all participants of the IDSA meeting.

FIFTH ANNUAL FALL CME COURSE SERIES

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

The fall course series will present recent advances in clinical HIV management through a mix of didactic lectures and clinically relevant cases developed by a distinguished panel of HIV/AIDS clinicians and researchers. Topics will include updates on HIV pathogenesis, new drugs and regimens, strategies for managing antiretroviral failure, and the changing course of HIV disease.

San Francisco, CA Friday, October 22, 1999
The Ritz-Carlton San Francisco
Chairs: Molly Cooke, MD, and Roy M. Gulick, MD, MPH
Early Registration Fee: $25

Los Angeles, CA Wednesday, November 3, 1999
Miramar Sheraton Hotel Santa Monica
Chairs: Ronald T. Mitsuyasu, MD, and Judith S. Currier, MD
Early Registration Fee: $25

EIGHTH ANNUAL WINTER/SPRING CME COURSE SERIES

Improving the Management of HIV Disease: An Advanced Course in HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management

The winter/spring CME program will review timely and clinically relevant issues in the management of HIV disease. Topics will include new insights in HIV pathogenesis, strategies for antiretroviral management, new antiretroviral drugs and regimens, long-term complications of antiretroviral therapy, and HIV resistance testing.

Atlanta, GA Friday, February 11, 2000
JW Marriott Hotel Lenox

Los Angeles, CA Saturday, February 26, 2000
Miramar Sheraton Hotel Santa Monica

New York, NY Wednesday, March 22, 2000
New York Hilton and Towers

Chicago, IL Wednesday, April 19, 2000
Hyatt Regency Chicago

Dates and locations to be announced for the following cities:
Boston, MA, San Francisco, CA, Dallas, TX.

For information about any of the courses, please contact the
International AIDS Society–USA

Symposium Voice Mail: (415) 561-6725
Fax: (415) 561-5740
E-mail: cme@iasusa.org

VOLUME 7, SEPTEMBER 1999