IMPROVING THE MANAGEMENT OF HIV DISEASE

IN THIS ISSUE—

Recent Advances In …

• HIV Pathogenesis

• Viral Load in Clinical Trials

• Issues in Adherence

• Pain Management
ABOUT THIS ISSUE...

This issue of Improving the Management of HIV Disease highlights selected presentations in the 1997 advanced CME courses. At the Los Angeles and Atlanta courses (February), Dr H. Clifford Lane discussed some of the recent insights in the immunopathogenesis of HIV disease, including new information on chemokine receptors and their role in HIV infection of target cells. Dr Steven Miles reviewed the crucial role of plasma viral load in monitoring HIV disease at the Los Angeles course, and discussed how clinical trial data on viral load relate to the clinical assessment of new antiretroviral regimens. The availability of potent antiretroviral regimens has provided new treatment opportunities for people with HIV disease. As discussed by Dr Gerald Friedland at the New York course (March), the complexity of these regimens requires an increased focus on strategies to maximize the benefits of these treatments in the clinic. Finally, Drs William Breitbart and Mathew Leikowitz provided reviews of the importance of the appropriate management of pain in patients with HIV and AIDS. This issue is the first of several that summarize presentations in the 1997 courses. These programs were made possible by the generous grant support provided by the commercial companies listed below.

The 1997 CME courses represented the fifth year of International AIDS Society–USA “Advanced Courses on HIV Pathogenesis, Antiretrovirals, and Selected Opportunistic Infections.” The courses are intended to provide summaries of the most recent clinical and basic scientific findings, with the goal of bridging clinical research and patient care.

The mission of the International AIDS Society–USA is to improve the treatment, care, and quality of life of persons with HIV/AIDS through balanced, relevant, and innovative education and information for physicians. Meeting this mission requires ongoing guidance from experts in the field in designing the academic content of our programs, and requires feedback from course attendees on the quality and relevance of the activities. In this regard, the program committees and advisory boards will meet shortly to develop the academic agendas for the Fall 1997 and the 1998 programs.

Following is information about the upcoming and planned International AIDS Society–USA-sponsored activities. Additional information about any of these programs can be requested by phone (415-675-7430), fax (415-675-7438), e-mail (IASUSA1@aol.com), or mail (at the address listed on the next page).

UPCOMING PROGRAMS AND REPORTS


The International AIDS Society–USA Antiretroviral Guidelines Panel first convened in January 1996, and its initial recommendations for the use of antiretroviral therapy were published in mid-1996 (Carpenter CC, et al. JAMA. 1996). The Panel has continued to meet on an ongoing basis to consider (continued on page 10)

Unrestricted educational grants supported the 1997 advanced CME courses and this issue. We gratefully acknowledge:

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- Glaxo Wellcome Inc.
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IMPROVING THE MANAGEMENT OF HIV DISEASE

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HIV PATHOGENESIS

HIV pathogenesis was discussed at the Los Angeles and Atlanta courses by H. Clifford Lane, MD, from the National Institutes of Health, Bethesda, Maryland.

Recent studies in viral dynamics, host immune response, and the regenerative ability of the immune system have yielded a substantial amount of information on pathogenesis of HIV infection. Studies of HIV replication and survival dynamics, detailed investigation of the architecture of lymphoid tissue in infection, and studies of CD4+ lymphocyte dynamics have demonstrated that HIV infection is a dynamic process of continuous viral replication (see accompanying article). Disparate lines of investigation have merged in the discovery of coreceptors to HIV and research has characterized a progressive decrease in the size and diversity of the CD4+ lymphocyte pool.

Susceptibility to Infection

The identification of factors that may influence susceptibility to infection upon exposure is the subject of much ongoing research. Building on the early work of Gallo et al on chemokines as anti-HIV factors and of Berger et al on a coreceptor with CD4 that mediated fusion, fusin was identified as a coreceptor for viral entry for the T-cell-tropic (syncytium inducing [SI]) isolates of HIV and of the β-chemokine receptor CCR5 as the coreceptor for the primary isolates of the macrophage-tropic (non-SI) phenotype isolates of HIV. In a study by Berger et al, CD4+ cells transfected with fusin are easily infected with the T-cell-tropic isolates of HIV-1 (LAV, HTLV-IIIB and RF), however, these cells lines could not be infected with macrophage-tropic isolates. Similarly, if CD4+ cells are transfected with CCR5, they can be easily infected with macrophage-tropic strains but not T-cell-tropic strains. The chemokine receptors are 7-transmembrane, G-protein coupled receptors. CCR5 is the physiological receptor for the cysteine-cysteine (CC) linked β-chemokines, RANTES, MIP-1α, and MIP-1β. Fusin is the receptor to SDF-1, a CXC chemokine (see Figure 1).

Since macrophage-tropic isolates are the more prevalent isolates in patients, it may be possible to use a congener of the ligand as a therapeutic agent.

The identification of coreceptors in part explains why some people, despite multiple high-risk behaviors, do not become infected with HIV. Genotypic analyses identified that some of these high-risk uninfected individuals are homozygous for deleted alleles of the CCR5 gene. The frequency of this mutation, a 32 base-pair deletion, is estimated at 11% in the Caucasian population and 1.7% in the African-American population. The homozygous genotype appears to confer resistance to HIV-1 infection. In a cohort of 1343 HIV-positive and 612 HIV-negative patients, none of the HIV-positive patients were homozygous for the Δ32 CCR5 mutation compared with 3% of the HIV-negative patients.

The heterozygous genotype does not appear to have an effect on resistance to infection; several studies have shown a consistent, but minor difference in the rate of disease progression between patients with the heterozygous Δ32 mutation and those with no mutation.

Disease Progression

The strength of the immune response to acute HIV infection appears to have a long-term impact on the course of the disease. Those patients who are able to control the virus well, as evidenced by low plasma HIV RNA levels and diverse T-cell responses, advance to clinical disease much more slowly than do those with high plasma HIV RNA levels (eg, >100,000 copies/mL) and a more restricted immune response. Nevertheless, the majority of patients eventually exhibit disease progression. A small proportion of patients—estimated by Dr Lane at probably less than 5%—do not appear to progress. “Long-term nonprogressors” have been the focus of much recent study that has attempted to characterize the immune effector mechanisms of such an apparently potent and enduring response to infection.

Much of the work done in the area of nonprogression has been descriptive and has thus far failed to adequately characterize the mechanisms underlying the phenomenon. In general, those persons categorized as long-term nonprogressors have lower levels of plasma HIV RNA and broader T-cell immune responses, ie, more CD8+ T-cell clones, than do persons who progress more rapidly. In fact, long-term nonprogressors do not constitute a discrete subset of patients; Dr Lane maintained that it is more likely that “nonprogression” is part of a continuum of responses ranging from very rapid to very slow progression.
He cited data from a study in Multicenter AIDS Cohort Study (MACS) patients that showed that those who maintained relatively stable CD4+ cell counts over the first several years of HIV disease still exhibited a characteristic decline in counts in subsequent years. In that study, a cohort of 56 patients who had been identified as long-term nonprogressors on the basis of follow-up over the first 7 years, during which they exhibited a mean CD4+ lymphocyte count increase of 18 cells/µL per year, were found to have a mean decrease of 67 cells/µL per year over the following 5 years—a rate of decline comparable to that observed in patients exhibiting a more typical infection course.

**CD4+ Lymphocyte Dynamics**

Studies of CD4+ lymphocyte dynamics in HIV infection have shown that the immune system is in a state of constant turnover far greater than under normal conditions. This phenomenon is readily demonstrated by the rapid increases in CD4+ cell counts following initiation of effective antiretroviral therapy and by measuring the fractions of CD4+ cells that are in the S phase (actively preparing to divide) at any given time.

Despite the increased production of CD4+ cells during HIV infection, there is a steady decline in the number of CD4+ cells over time. Along with this quantitative change, there are qualitative changes that have profound implications for treatment. Studies of changes in "naive" and "memory" CD4+ lymphocyte populations, analyses of the survival and distribution of genetically marked CD4+ lymphocytes, and analyses of specificity-mapping of the CD4+ lymphocyte receptor repertoire all support the conclusions that (1) elements of the T-cell repertoire are lost during progressive infection, and (2) increases in cell counts observed during treatment represent expansion of the remaining elements of the repertoire rather than addition of new or reacquisition of lost elements.

**Naive and Memory Cell Dynamics**

Antigen specificity of CD4+ lymphocytes is conferred by expression of α/β heterodimers on the cell surface—the T-cell receptors. CD4+ lymphocytes can be phenotypically characterized as "naive" or "memory" on the basis of CD45R isoform expression: those cells that have a high molecular-weight isoform (CD45RA) are termed naive, while those with a low molecular-weight isoform (CD45RO) are referred to as memory cells. Naive CD4+

In initial studies, loss of ability to respond to recall antigen suggested that memory cells were selectively lost.

T lymphocytes have a long half-life (>10 years), do not exhibit effector functions, and express L-selectin, an adhesion molecule that facilitates binding to the lymph node high endothelial venules. The memory T cells have a shorter half-life (1 year), exhibit effector functions, and express adhesion molecules that facilitate binding to tissues (LFA-1,3 and α4, α5, α6, and β1 integrins).

When T cells exit the thymus, they all bear the high molecular-weight isoform. Through selection processes in the thymus, each cell is "programmed" to respond to a specific potential antigen. Thus, although each cell has a unique specificity, the total cell population produced represents a possible response to an enormous number of different potential antigens. As the cells encounter the antigen for which they are specific (eg, in early life), the CD45 gene undergoes differential splicing in such a way that the low molecular-weight isoform comes out on the cell surface, with clonal expansion of the memory cell. In any individual, the total T-cell population comprises naive cells and memory cells, with the character of the overall system gradually reflecting the specific antigenic environment of that individual. These phenotypes, however, are not stable: naive cells can become memory cells after they encounter their specific antigen, and memory cells can revert to naive cells if they do not encounter antigen.

In initial studies in AIDS patients, a loss of ability to respond to recall antigen was observed, suggesting that memory cells were selectively lost. However, it subsequently has been demonstrated that the proportion of naive CD4+ cells declines as overall CD4+ counts decline (Figure 2); it has been postulated that only memory cells remain by the end stages of HIV infection. Dr Lane noted that this phenomenon is similar to what is observed in normal aging, suggesting that HIV infection might be likened to an accelerated immune senescence.

With the use of the CD45 marker, characteristics of the CD4+ cells produced

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**Figure 2. Changes in Naive and Memory CD4+ Cells During Progressive HIV Infection.** Data from 40 patients followed for several years showing relative proportions of naive and memory cells during progressive HIV infection. Adapted from Nature Med. May 1997.
However, a number of findings suggest that in fact this is not the case. High-resolution CT scanning of the thymus during treatment-associated increases in CD4+ cell counts has shown increases in both naive- and memory-cell populations despite involution of the thymus. In one example presented by Dr Lane, an increase in CD4+ cell counts from approximately 50/µL to more than 500/µL was not accompanied by thymic hyperplasia or other evidence that the cells originated from the thymus (Figure 3). Labeling of existing cells with a genetic marker has shown that the proportion of marked cells remains constant throughout the expansion of the population, indicating that the increase in cell numbers can be explained by expansion of existing circulating cells, not entry of new cells from the thymus.

Polymerase Chain Reaction (PCR) Studies of T-cell Receptor Families

Other data demonstrating that loss of elements of the T-cell repertoire occurs during HIV infection come from PCR studies of T-cell receptor repertoires. A number of different subsets of T cells are produced by rearrangement of the T-cell receptor gene after stem cells enter the thymus. Some of these subsets can be recognized by distinctive T-cell receptor variable region β (Vβ) chains. A total of 24 different types of Vβ chains has been identified, each of which gives rise to T-cell receptors of 8 different sizes, producing a total of 192 different T-cell receptor families. Selective PCR amplification of the Vβ chains allows mapping of the distribution of the different T-cell receptor types. Figure 4 shows the results of such studies in syngeneic twins discordant for HIV infection. Such results indicate that HIV infection is associated with a severe disruption of CD4+ lymphocyte repertoire. This disruption does not appear to be reversed, at least over the short term, by effective antiretroviral treatment. Figure 5 shows the distribution of receptor families for 3 Vβ chains before and after treatment with a protease inhibitor and interleukin-2, which resulted in an increase in CD4+ cell counts from 238/µL to 1102/µL.

The determinants of the quality of the CD4+ lymphocyte pool in the context of HIV infection can be understood schematically (see Figure 6). Cells leave the pool both through death as part of the natural remodeling of the immune system and through HIV-induced death. Cells can enter the pool by stem-cell differentiation and processing in the thymus in early life or by somatic cell division. In adults, regardless of whether HIV infection is present, the entry of new cells appears to play little, if any, role; the division of cells already existing in the pool accounts for all replenishment of cells lost through natural or other death. Thus, it appears that if diversity within the existing pool is lost in the adult, it is not likely to be replaced, at least during the short term. According to Dr Lane, the T cells of the immune system can be viewed as the tiles in a game of Scrabble. In the normal aging process, a memory pool is generated of the letters that are commonly needed; the crucial part of the immune system resides in the memory pool. Some of the naïve pool is retained, analogous to the letters that are not
Pathogenesis

Pre-therapy
CD4+ = 238 cells/μL

Post-therapy
CD4+ = 1102 cells/μL

Vβ5

Vβ6

Vβ8

Figure 5. Disruption of the CD4+ T-Cell Repertoire Is Not Reversed by Treatment With Protease Inhibitor + IL-2. T-cell-receptor repertoires for three variable region β chains (Vβ) in an HIV-infected patient before and after treatment with a protease inhibitor and interleukin-2, which resulted in an increase in CD4+ cell count from 238 cells/μL to 1102 cells/μL. Despite the increase in CD4+ count, no change is observed in receptor repertoires for Vβ5 or Vβ8 chains. For Vβ6, the tallest peak under normal conditions would be that two peaks to the left of the tallest one in this patient both prior to and after therapy. Although some change in receptor repertoire is observed, the skewing of the distribution observed before therapy persists after treatment.

 used as often. As HIV progresses, there are fewer letters and fewer different letters. As Dr Lane noted, it is still possible to communicate with these fewer letters, but far more difficult.

Summary

Current understanding of viral and immune system dynamics can be summarized as follows: (1) HIV infection is characterized by ongoing viral replication that leads to progressive depletion of CD4+ lymphocytes with preferential loss of "naive" cells. (2) This viral replication is driven by the number of productively infected cells and is associated with an increased turnover of CD4+ lymphocyte. (3) As the CD4+ lymphocyte pool is quantitatively reduced, there is a progressive and irreversible loss in immunologic diversity. Dr Lane emphasized that these data all point to the importance of early therapeutic intervention in patients with HIV infection.

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Figure 6. The CD4+ Lymphocyte Pool. The CD4+ lymphocyte pool is depleted by natural and HIV-induced cell death; in adults, the pool is replenished by somatic cell division.

Suggested Readings


Recent findings on plasma viral load and the practical aspects of using viral load data in the clinical setting were discussed at the Los Angeles course by Steven A. Miles, MD, from the University of California Los Angeles.

**The Use of Viral Load Measurements as Prognostic and Therapeutic Markers**

In the last year, the use of viral load assays to measure HIV RNA in plasma has become recognized as an essential part of clinical management for patients with HIV disease. One viral load test, a quantitative reverse transcriptase polymerase chain reaction (RT PCR) test can dependably detect 500 or more copies of HIV RNA/mL of plasma and has been approved by the FDA for diagnostic and 36,000, and 19,000 copies/mL at 60, 90, 120, and 180 days, respectively. Considerable intersubject variation was observed at all time points. In patients from whom samples were obtained within 6 months of seroconversion, clinical and immunologic progression was not related to the plasma HIV RNA level. After approximately 6 months a steady state “set point” appears to be established. In one study, the plasma HIV RNA level at the post-seroconversion set point level (>6 months after seroconversion) was highly predictive of clinical progression and was related to the risk of death.

Viral load measurements are also valuable in measuring the kinetics of viral and T-cell replication in response to antiretroviral therapy. There is a two-phase viral decay slope, with a 90% to 99% reduction in plasma viral load in the first two weeks of therapy, and a slower second-phase decline to undetectable levels over the next 12 to 24 weeks. This second phase reflects the slower clearance of chronically infected T cells or macrophages.

With potent combination therapies, many patients achieve a level of plasma viral RNA below the limit of detection of the available assays. Newer generation bDNA and RT PCR research assays, which can detect as little as 20 to 50 copies of HIV RNA/mL of plasma have confirmed that “undetectable” does not necessarily indicate “no viral replication.” Further, while the virus may be undetectable in the plasma, it may be present in the central nervous system, the lymph nodes, the bone marrow, and other body compartments.

The limits of currently available assays in detecting low levels of plasma HIV RNA complicates the ability to completely assess the effectiveness of antiretroviral regimens and to identify initial failure. The “duration of maximal viral suppression,” a term borrowed from oncology, is defined as the time between the trough value for the plasma HIV RNA level and two subsequent values (measured at least four weeks apart) that are at least 0.3 log greater than the trough value. In the studies of ritonavir, the durability of the HIV RNA level response was predicted by the trough value, not by the magnitude or rate of the plasma HIV RNA decline. Thus, with the protease inhibitors, the minimum plasma HIV RNA value achieved with therapy may serve as a prognostic indicator for time to eventual viral rebound.

Clearly, viral load assays are important and powerful tools, but many questions remain about optimal clinical use. Understanding the value and limitations of the assays will help to avoid premature discontinuation of still-effective antiretroviral regimens. Familiarity with logarithms.

### Table 1. Decimal, Exponent, and Logarithms

<table>
<thead>
<tr>
<th>Decimal Number</th>
<th>Exponential Form</th>
<th>Log10 Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>100,000,000</td>
<td>(10^8)</td>
<td>8</td>
</tr>
<tr>
<td>10,000,000</td>
<td>(10^7)</td>
<td>7</td>
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<td>1,000,000</td>
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<tr>
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<td>(10^3)</td>
<td>3</td>
</tr>
<tr>
<td>100</td>
<td>(10^2)</td>
<td>2</td>
</tr>
</tbody>
</table>

*Each number is a tenfold change from the previous*
knowledge of factors that effect plasma viral load, and the ability to assess clinical trial data critically all contribute to optimal use of these assays.

**Clinical Use of Viral Load Measurements**

**Interpreting Logarithmic Data**

Several general strategies can simplify the use of viral load data. Table 1 lists decimal numbers, the exponential forms, and the logarithmic equivalents. To calculate a 1-log increase or decrease, add or remove, respectively, the last digit (e.g., 1-log decrease from a value of 10,000 is a decrease to 1000). To determine if two plasma HIV RNA values are significantly different, calculate whether there is a threefold difference between them (e.g., 150 copies/mL to 50 copies/mL represents a significant decline). While these strategies may help in comparing serial viral load measurements, it is important to emphasize that the target viral load value is unequivocally zero.

**Factors That Influence Viral Load Measurements**

A number of immunologic stimuli, including secondary viral infections such as reactivation of herpes simplex virus; opportunistic infections; influenza; and vaccinations may increase viral load and confound viral load measurements. Suppressing opportunistic or other infections, with the resulting decline in cytokine levels, decreases plasma HIV RNA levels. Other factors that are known to increase viral replication are blood transfusions and poor patient adherence to the drug regimen. One plasma HIV RNA value at any given point in time is difficult to interpret; the ability to assess a patient’s response to a drug regimen requires multiple sequential measurements. According to Dr. Miles, if a laboratory value indicates increased viral replication, particularly a modest increase of 0.5 to 0.7 log, it is important to consider laboratory error, a transient intervening influence such as a secondary infection, and poor patient adherence before changing the antiretroviral regimen.

One common clinical question is the value of influenza vaccine for patients with HIV. According to Dr. Miles, while the vaccine is likely to increase HIV replication, an episode of influenza is likely to cause a greater increase. Thus, if a patient is likely to be exposed to influenza, the vaccine is recommended.

**Evaluating Virologic Response Data From Clinical Trials**

Interpreting virologic response data from clinical trials of antiretroviral therapy is challenging due to the number of factors that can be incorporated into, or not be included in, any particular analysis. According to Dr. Miles, four pieces of information are critical: 1) the sensitivity of the assay (e.g., what is the limit of detection of the method used); 2) the pretreatment viral load; 3) the median decrease in plasma HIV RNA; and 4) the number of patients at each measurement interval (see Table 2).

**Conclusions**

New generations of viral load tests with greater sensitivity will enable providers and patients to more accurately assess the viral burden and the potency of various antiretroviral therapies. In the near future, proviral DNA assays, which can determine the level of integrative virus, may be used for viral testing in patients with undetectable levels of plasma HIV RNA. At present, however, the available assays provide invaluable markers of disease progression and response to antiretroviral therapy.

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**Suggested Readings**


Hubert JB, Meyer L, Dussaix E, et al and the SEROCO Study Group. Prognostic value of early HIV-1 RNA levels on disease progression in 363 patients with a known date of infection. Presented at the 4th (continued)
Suggested Readings (continued)

Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract 478.


(new from inside front cover)

new pathophysiologic and clinical trial data and how they revise the recommendations; its updated report may be available soon. A reprint of the report will be included in the next issue of this publication.

Clinical Dilemmas in HIV Disease Management: An Advanced CME Course

Until this year, the International AIDS Society–USA Fall CME program has presented a full day of lectures on the prevention and management of the opportunistic diseases and other manifestations of advanced-stage HIV disease. The format and the agenda have changed substantially this year.

The revised program will use specific case presentations to illustrate current clinical dilemmas and their management. The cases will cover issues in the clinical management of HIV disease that range from antiretroviral management to the treatment of specific opportunistic infections. Common themes throughout the case presentations will include drug-drug interactions, issues of viral resistance to drugs, toxicity management, and others.

The cases are being developed for presentation by an expert panel of 18 clinicians and investigators. Symposia will be scheduled for the fall of this year (September and October); program brochures and schedules will be available in July.

HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management: Sixth Annual Advanced Course Series

The 1998 program agenda for the sixth annual course series will be developed shortly. In general, new insights in HIV pathogenesis, recent data from clinical trials that evaluate new antiretroviral drugs and combinations, discussions of the appropriate strategies for initiating and changing antiretroviral treatments, and updates on the management of specific opportunistic infections will be discussed at the programs.

The CME courses will be held in Los Angeles, Atlanta, New York, Chicago, San Francisco, and other cities, and will be scheduled between February and May 1998.

National Course on HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management

Next year, in addition to the full-day CME programs described above, a four-day, national meeting will be held as part of the sixth annual course series.

The course will cover relevant new research results and their applications to clinical practice. The course is tentatively scheduled for March 25-29, 1998, in Colorado.

Registry for Physicians Who are Actively Involved in HIV/AIDS Care

A Registry of HIV-treating physicians is being developed. Please refer to the information on the back page of this issue for more information.

Recommendations for Treatment for CMV Diseases

A 17-member expert panel has been convened by the International AIDS Society–USA to develop guidelines for the treatment of CMV end organ diseases. The panel met in April of this year, and is preparing its report. A reprint of the report will be sent to subscribers of this publication.

Improving the Management of HIV Disease

This publication will continue to provide reviews of clinically-relevant topics, special articles, and new features. If you wish to continue your complimentary subscription this year, please complete and return the form on the back page of this issue.
AUDIOTAPES OF IAS-USA PRESENTATIONS:
Improving the Management of HIV Disease Presentations

Based on numerous requests from symposium participants, audiotapeces of the symposium presentations are available for purchase. Each unedited individual presentation audiotype is approximately 30 minutes in length. The following lists presentations from upcoming courses (tapes will not be available until one week after the course). To order, check the box(es) corresponding to the tape(s) you wish to purchase and send the completed order form with payment to the address listed at the end of this form.

ATLANTA, GEORGIA, FEBRUARY 13, 1997
Chair: MICHAEL S. SAAG, MD
Co-chair: MELANIE A. THOMPSON, MD
HIV Pathogenesis
H. Clifford Lane, MD ............................................
HIV Quantitation In Vivo: Use in Clinical Practice
Robert T. Schooley, MD ...........................................
Antiretroviral Resistance
Victoria Johnson, MD ............................................
Recent Clinical Trial Results: New Antiretroviral Drugs and Combinations
Melanie A. Thompson, MD ........................................
Approaches to the Prevention and Management of HAART Failure
Michael S. Saag, MD .............................................
Prevention and Treatment of CMV Infections
Kathleen Squires, MD ............................................
Prevention and Treatment of Fungal Infections in Patients with AIDS
William G. Powderly, MD ........................................
Strategies for the Prevention and Treatment of Mycobacterium avium Complex Disease
C. Robert Horsburgh, Jr., MD ....................................

LOS ANGELES, CALIFORNIA, FEBRUARY 22, 1997
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Co-chair: PAUL A. VOLBERDING, MD
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Results of Clinical Trials of New Anti-HIV Drugs and Combinations
Paul A. Volberding, MD ...........................................
Approaches to the Prevention and Management of HAART Failure
Michael S. Saag, MD .............................................
New Antiretroviral Strategies Under Investigation, Current Research Questions, and Issues in Resistance
Douglas D. Richman, MD ........................................
Alexandra M. Levine, MD ........................................
Issues and Strategies in Adherence to Treatments of HIV Disease
Gail Wyatt, PhD ...................................................
HIV Pathogenesis
H. Clifford Lane, MD ............................................
Immunomodulation in HIV Infection
Ronald T. Mitsuyasu, MD ........................................

NEW YORK, NEW YORK, MARCH 7, 1997
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Co-chair: PAUL A. VOLBERDING, MD
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David D. Ho, MD ................................................
Use of Virologic Markers in Clinical Practice
Michael S. Saag, MD .............................................

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Donna Mildvan, MD ................................................
Update of the International AIDS Society–USA Antiretroviral Guidelines
Paul A. Volberding, MD ...........................................
HIV Therapeutics, Clinical Trials and Tribulations: Efficacy Versus Effectiveness
Gerald H. Friedland, MD ........................................
Prophylaxis for Opportunistic Infections in the Era of Highly Active Antiretroviral Therapy (HAART)
Judith S. Currier, MD ............................................
Systemic Therapeutic Options for Cytomegalovirus Retinitis
Elizabeth L. Cooney, MD ........................................
Cytomegalovirus Retinitis: Intravitreal Therapy
Ray F. Garino, MD, PhD .........................................
Managing Managed Care and Managing HIV-Infected Patients: Are They Mutually Exclusive?
Douglas T. Dieterich, MD ........................................

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Co-chair: ROBERT T. SCHOOLEY, MD
Drug Resistance: Out of the Lab and into the Clinic
Daniel R. Kuritzkes, MD ........................................
Antiretroviral Chemotherapy: New Drugs and New Approaches
Robert T. Schooley, MD ...........................................
HIV-1 Co-Receptors: Their Role in Viral Entry into CD4+ T Cells
John P. Moore, PhD ..............................................
Management of HIV-exposed Healthcare Workers
Harold A. Kessler, MD ............................................
Antiretroviral Therapy: Pharmacokinetics and Drug Interactions
Juan J.L. Lertora, MD, PhD ......................................
Neurologic Complications of HIV Infection
David B. Clifford, MD ............................................
Management of Cytomegalovirus Infections
Richard B. Pollard, MD ...........................................
Lessons From a Fatal Case of Tuberculosis
Newton E. Hyslop, Jr., MD ......................................
Disseminated Mycobacterium avium Complex Disease in Patients with AIDS
Constance A. Benson, MD .......................................

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Co-chair: STEPHEN E. FOLLANSBEE, MD
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James O. Kahn, MD ..............................................
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(SAN FRANCISCO continued)
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Ashley T. Haase, MD .................................................. □
Immune Reconstitution After Highly Active Antiretroviral Therapy (HAART)
Michael M. Lederman, MD ........................................... □
Recent Results and Insights From Drug and Combination Trials
Julio S. G. Montaner, MD, FRCP, FCCP .................................. □
New Approaches to the Prevention and Management of HAART Failure
Michael S. Saag, MD .................................................. □
New Antiretroviral Therapies: Adherence Challenges and Strategies
Margaret A. Chesney, PhD .............................................. □
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ADHERENCE: THE ACHILLES’ HEEL OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

At the recent New York course, Gerald H. Friedland, MD, from the Yale University School of Medicine in New Haven, Connecticut, discussed adherence as a key factor in extending the benefits observed with aggressive combination therapy in clinical trials to the practice setting.

Advances in HIV pathogenesis and viral dynamics, and the availability of viral load assays and potent antiretroviral drug regimens have provided new opportunities to treat patients with HIV disease. Combined aggressive antiretroviral therapy has enormous potential to delay disease progression and death. However, achieving this potential in the practice setting involves addressing the complex behavioral issue of compliance/adherence. Despite different connotations, the terms “compliance” and “adherence” are currently used interchangeably. Adherence is perhaps the more accurate term in that it indicates patient choice in medication taking, but compliance is in more common usage.

Efficacy vs Effectiveness

The term efficacy is used to characterize the definable benefits from a drug or a combination of drugs; measures of efficacy are specific, clearly defined, and usually derived from a controlled clinical trial. Effectiveness, however, refers to how a drug or combination of drugs works in the real world.

In the structure of clinical trials, information derived from clinical trials may not necessarily translate well to clinical practice.

Clinical trials are designed to enroll highly-selected populations and the findings are often difficult to generalize to the larger, more diverse patient population in clinical practice. Patients with medical issues such as liver function abnormalities, renal failure, alcoholism, and substance abuse, while common in clinical practice, are excluded from most drug trials. In part due to the maturity of the HIV epidemic, patients presenting in the clinical setting are often heavily pretreated, and have advanced disease. In addition, the behavioral characteristics of patients who enroll in clinical trials differ from those of patients who do not. In a study conducted by Ethier and colleagues at Yale, investigators assessed characteristics of patients in clinical trials, those interested in participating in clinical trials, and those declining participation. Patients choosing to enroll in clinical trials were more likely to be able to keep track of time, to be able to adapt their lifestyle to treatment regimens, and to believe that the value of the drug outweighed the inconvenience of the number of pills involved, and were less fearful of potential of side effects.

Adherence to Treatment Regimens

Studies in the disease areas of hypertension, epilepsy, tuberculosis, and in the geriatric population have demonstrated 1) adherence to drug regimens is poor across populations and diseases; 2) providers cannot predict who will or will not adhere to drug regimens; and 3) providers consistently overestimate patients’ adherence to recommended drug regimens.

Clearly, the degree of adherence to therapy affects treatment outcome; low adherence reduces both efficacy and toxicity. Importantly, in the field of HIV disease poor adherence promotes the opportunity for the development of viral resistance. If a patient takes very little or no drug, the likelihood of resistance is relatively low because there is little or no pressure to select a resistant mutant. In theory, if adherence is complete (100%) with potent combination therapy, viral replication will most likely be halted and resistant viral mutants are unlikely. However, in patients who intermittently or irregularly take drugs (the majority of patients in clinical practice setting), the likelihood of selection of mutants that are resistant to the drug(s) increases, a consequence of both continuing viral replication and selective antimicrobial pressure.

Determinants of Adherence

As shown in Table 1, adherence to medication has multiple, overlapping determinants. In terms of patient characteristics, social support is probably the most important factor. The literature on adherence strongly and consistently demonstrates that adherence cannot be predicted based

<table>
<thead>
<tr>
<th>Table 1. Factors That Affect Adherence</th>
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</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
</tr>
<tr>
<td>- Knowledge</td>
</tr>
<tr>
<td>- Social support</td>
</tr>
<tr>
<td>- Beliefs</td>
</tr>
<tr>
<td>- Trust in provider</td>
</tr>
<tr>
<td>- Demographic characteristics</td>
</tr>
<tr>
<td><strong>Treatment regimen</strong></td>
</tr>
<tr>
<td>- Number of medications</td>
</tr>
<tr>
<td>- Frequency of dosing</td>
</tr>
<tr>
<td>- Complexity</td>
</tr>
<tr>
<td>- Duration</td>
</tr>
<tr>
<td>- Side effects</td>
</tr>
<tr>
<td>- Degree of behavioral change required</td>
</tr>
<tr>
<td><strong>Patient-provider relationship</strong></td>
</tr>
<tr>
<td>- Trust</td>
</tr>
<tr>
<td>- Consistency</td>
</tr>
<tr>
<td>- Level of supervision</td>
</tr>
<tr>
<td>- Similar demographic characteristics</td>
</tr>
</tbody>
</table>
solely on age, race, sex, or educational status. Addressing individual health beliefs, and understanding the individuals risk-benefit equation is a key in influencing adherence. Aspects of the patient-provider relationship, including trust, consistency, and continued interaction are also important determinants of adherence. In a study by Altice and colleagues conducted among prison inmates with HIV disease, a scale designed to measure trust in physician was used to demonstrate that increased trust was associated with both increased acceptance of and adherence to antiretroviral medication. Characteristics of the treatment regimen also predict adherence. Increasing number of pills, frequency of dosing, duration of therapy, and frequency of side effects all decrease the likelihood of adherence.

**Measuring Adherence**

Four methods are commonly used to measure adherence: self-report (questionnaire/interviews/diary), pill count, drug assay, and electronic monitoring. Pill counts have been used extensively but are not believed to be accurate; patients may empty the pill box, or take all of the remaining pills before their clinic visit. The accuracy of drug assays depends in part on the half-life of the drug; longer-acting indicators have been used, but testing will show only past ingestion and not frequency or dosing interval.

The Medication Event Monitoring System (MEMS) provides a computer chip in the cap of the medicinal bottle; information is recorded each time the bottle is opened. Figure 1 is an example of MEMS data, and shows the wide variation in adherence patterns for four patients given didanosine therapy. Data from the MEMS allows calculation of 1) the adherence rate, or percentage of pills taken; 2) prescribed frequency; and 3) prescribed interval. A small study of adherence in patients taking antiretroviral therapy revealed that while the overall adherence rate (fraction of doses taken) was 82% to 86%, more detailed measures of the fraction of doses taken at the prescribed daily interval (55%-76%) and fraction of doses taken at the prescribed dosing interval (27%) were lower.

**Interventions to Improve Adherence**

Table 2 lists strategies for improving adherence to drug therapy. As noted earlier, social and technical support from partners, family members, and health care providers are important elements for enhancing adherence.

**Conclusion**

Impressive gains have been made in the ability of antiretroviral therapy to suppress viral replication and delay disease progression in patients with HIV. However, given the current recommendations to use highly aggressive combination therapy, drug options remain limited. In order to replicate the findings observed in clinical trials of these combinations, and to maximize the potential of each drug, targeted efforts to increase adherence in the real world clinical setting are essential.

Gerald H. Friedland, MD, is Professor of Medicine, Epidemiology, and Public Health at the Yale University School of Medicine, and Director of the AIDS Program at Yale New Haven Hospital in New Haven, Connecticut.
Suggested Readings


Cotton D, Finkelstein D, He W, Feinberg J. Determinants of accrual of women to a large multicenter clinical trials program of human immunodeficiency virus infection. The AIDS Clinical Trials Group. JAIDS. 1993;6:1322-1328.


Wright EC. Non-compliance or how many aunts has Matilda? Lancet. 1993;342:909-913.

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PAIN MANAGEMENT IN HIV DISEASE

Pain is common in persons with advanced HIV disease. It has many causes and presentations. Many physicians may tend to minimize the pain that HIV-infected patients experience. The management of pain in HIV disease was discussed by William Breitbart, MD, in New York and by Mathew Lefkovitz, MD, in Los Angeles. In their presentations Drs. Breitbart and Lefkovitz emphasized that pain in HIV disease is often undertreated and reviewed the extensive HIV-related pain syndromes, the existing guidelines for assessing and managing this pain, and the analgesic and other agents that are available for treating it.

Pain is highly prevalent and dramatically undertreated in patients with HIV disease. The prevalence increases as the disease progresses; data from various studies indicate that clinically significant pain occurs in approximately 25% of patients with early HIV disease, in 50% of ambulatory patients with AIDS, and in 90% or more of patients in hospice and palliative care units. With an intensity comparable to that of cancer pain, HIV-related pain is associated with significant psychological, functional, and physical morbidity.

Pain Syndromes in HIV Disease

The pain associated with HIV disease is diverse in its presentations and causes; more than 100 distinct syndromes have been described in patients with HIV disease. Approximately 50% of these syndromes are related directly to the HIV infection or the associated opportunistic infections and neoplasms, approximately 30% are due to anti-HIV therapies or diagnostic procedures, and approximately 20% are not related to either HIV infection or the associated therapies (Table 1). The most common pain syndromes reported by patients with HIV disease are abdominal pain, peripheral neuropathy, oropharyngeal pain, headache, arthralgias and myalgias, painful dermatologic conditions, and back pain. In addition, there are painful gynecologic and pelvic syndromes that are unique to women with HIV disease.

Typically, two or three different pain syndromes are occurring simultaneously in patients with HIV-related pain. Approximately 40% of the pain syndromes in patients with HIV disease have neuropathic origins, resulting from damage to the peripheral nervous system. The remaining 60% of the pain syndromes are somatic or visceral in origin, resulting from damage to the skin, muscles, and soft tissue and from processes that involve the visceral organs of the abdomen.

Strategies for Managing Pain in HIV Disease

In developing an approach to managing pain it is important that clinicians understand that HIV-related pain, like cancer pain and other chronic pain, is multidimensional. More than just the physical phenomenon, the experience of pain includes cognitive aspects, such as the meaning of pain; emotional aspects, such as fear, anxiety, and depression; and socioenvironmental factors, such as social support, financial stability, and issues related to substance abuse. The psychosocial components of pain may be more pronounced in patients with HIV disease. One study by Breitbart and colleagues found significantly higher rates of depression, overall psychological distress, hopelessness, and suicidal ideation in patients with AIDS-related pain than in patients with pain that was related to other diseases. Patients with AIDS-related pain in this study who interpreted new occurrences of pain as progression of their HIV disease reported significantly greater pain intensity than those who saw no connection between their pain and progression of their disease.

An optimal approach to pain management is multidisciplinary, and includes pharmacologic therapy, cognitive/behavioral interventions, and psychosocial therapy (Table 2). Given limited resources, however, analgesic therapy can achieve adequate pain relief in only 80% to 85% of patients with HIV-related pain. This summary focuses on the pharmacologic management of pain.

Analgesic Therapy for Pain

Appropriate analgesic drugs can be selected with the aid of tools like the World Health Organization (WHO) Analgesic Ladder (Figure 1), which is based on principles developed over the last two decades for managing cancer pain. In the WHO Analgesic Ladder the assessment is based on the intensity and type of the pain. Intensity is typically assessed on a 1-to-10 scale. Treating patients with mild pain (1–3 score) would begin at the bottom of the ladder, with a nonopioid drug such as acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). Persistent or increasing pain or an initial presentation with moderate pain (4–7 score) would call for the use of a weak opioid (such as codeine, hydrocodone, or oxycodone) together with a nonopioid. If the
highly plasma protein-bound, to patients with advanced HIV disease. The incidence of toxic effects, including blood dyscrasias, increases in bleeding time, gastric damage, renal effects, and hepatic reactions, may be higher in patients with hypoproteinemia that is due to wasting. Acetaminophen is not as effective in HIV-related pain, and toxic effects occur at doses greater than 1000 mg q4h.

**Opioid Analgesics**

Opioid drugs are the basis for managing moderate to severe pain, and can be categorized as short-acting and long-acting. The dose and the schedule of administration depend on a number of factors, including the severity and type (nociceptive or neuropathic) of the pain, side effects, and individual patient tolerance.

Within the category of short-acting opioids, the weaker agents include hydrocodone and codeine. Codeine is commonly prescribed, but it has only a weak analgesic effect and is associated with constipation. Propoxyphene and opioid agonists/antagonists are not recommended. The stronger, short-acting opioids include morphine, oxycodone, and methadone. Methadone is an inexpensive alternative, with high bioavailability and a variable duration of analgesia. Meperidine is associated with a higher incidence of side effects, and may cause central nervous system (CNS) excitement, seizures, tremor, and multifocal myoclonus.

Patients who are taking 5 to 10 doses of short-acting opioids a day may have to be shifted to long-acting opioids, such as sustained-release morphine or sustained-release oxycodone, which provide analgesia for 8 to 12 hours. These drugs provide more-constant serum levels and facilitate convenient dosing and administration, which result in substantial psychological benefits. Sustained-release morphine sulfate is administered on a q12h schedule, but more-frequent dosing may be required in patients with AIDS because of their increased metabolic rate and the drug’s variability in absorption. Peak plasma concentrations are achieved in approximately 4 hours and steady-state levels in 1 to 2 days. In patients with a daily morphine requirement of less than 120 mg, sustained-release morphine sulfate should be initiated at a dose of 30 mg q12h. There is no evidence of drug accumulation, and the side effects are comparable to those with the immediate-release formulation.

The fentanyl transdermal system, which provides analgesia for up to 72 hours, is an alternative in patients who may not be able to tolerate additional oral medications. Fentanyl is effective for both nociceptive and neuropathic pain that cannot be managed with an acetaminophen/opioid combination, NSAIDs, or short-acting opioids in prn doses. Delivered through a microporous membrane, a fixed amount of fentanyl is absorbed into the skin, creating a reservoir that is available for systemic

### Freedom from AIDS pain

<table>
<thead>
<tr>
<th>Mild pain (level 1–3)</th>
<th>Pain persisting or increasing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate pain (level 4–7)</td>
<td>Pain persisting or increasing</td>
</tr>
<tr>
<td>Severe pain (level 8–10)</td>
<td>Pain persisting or increasing</td>
</tr>
</tbody>
</table>

**Figure 1.** The WHO Analgesic Ladder for Managing Pain. Adapted from WHO, Cancer Pain Relief, 1986.
Table 3. Analgesics for Managing Pain in HIV Disease and AIDS

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>Route</th>
<th>Dose (mg)</th>
<th>Duration (h)</th>
<th>Plasma half-life (h)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Aspirin</td>
<td>po</td>
<td>650</td>
<td>4-6</td>
<td>4-6</td>
<td>The standard for comparison among nonopioid analgesics</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>po</td>
<td>400-600</td>
<td>----</td>
<td>----</td>
<td>Like aspirin, can inhibit platelet function</td>
</tr>
<tr>
<td>Choline magnesium</td>
<td>po</td>
<td>700-1500</td>
<td>----</td>
<td>----</td>
<td>Essentially no hematologic or gastrointestinal side effects</td>
</tr>
<tr>
<td>trisalicylate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short-acting opioids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>po</td>
<td>32-65</td>
<td>3-4</td>
<td>----</td>
<td>Metabolized to morphine; often used to suppress cough in patients at risk for pulmonary bleeding</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>po</td>
<td>5-10</td>
<td>3-4</td>
<td>----</td>
<td>Available as a single drug and in combination with aspirin or acetaminophen</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>po</td>
<td>65-130</td>
<td>4-6</td>
<td>----</td>
<td>Toxic metabolite norpropoxy accumulates with repeated dosing</td>
</tr>
<tr>
<td><strong>Long-acting opioids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine,</td>
<td>po</td>
<td>90-120</td>
<td>8-12</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>sustained release</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Now available in long-acting, sustained-release forms</td>
</tr>
<tr>
<td>Oxycodone,</td>
<td>po</td>
<td>20-40</td>
<td>8-12</td>
<td>2-3</td>
<td></td>
</tr>
<tr>
<td>sustained release</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In combination with aspirin or acetaminophen it is considered a weaker opioid; as a single drug it is comparable to the strong opioids, like morphine</td>
</tr>
<tr>
<td>Fentanyl system</td>
<td>transdermal</td>
<td>.025</td>
<td>48-72</td>
<td>2-3</td>
<td>Transdermal patch is convenient, bypassing GI analgesia until depot is formed; not suitable for rapid titration</td>
</tr>
</tbody>
</table>

circulation. Because analgesic levels of the drug are not reached until 12 hours after the patch has been applied, and because the dose cannot be adjusted immediately, it is important to provide patients with short-acting opioids for breakthrough pain. A number of factors, including high fever, broken skin beneath the patch, and low body fat, increase the rate of reservoir depletion and limit the duration of analgesia.

**Adjuvant Drugs**

At each step in the analgesic ladder the use of adjuvant drugs is an option; some selected drugs are listed in Table 4. The adjuvant drugs include antidepressants and anticonvulsants, which are used primarily in treating neuropathic pain, and various other drugs that are used to prevent or counteract the side effects of opioid drugs.

The antidepressants potentiate the analgesic effects of opioid drugs and also have an independent analgesic effect. These agents function by altering the level of neurotransmitters, such as serotonin and norepinephrine, in the central nervous system and through direct effects on damaged nerves, e.g., by decreasing the paroxysmal discharges of damaged nerves and decreasing the sensitivity of adrenergic receptors on budding nerve sprouts. The tricyclic agents have been studied most extensively for pain relief, and are first-line therapy for burning, tingling, and numbing neuropathic pain. The onset of their analgesic effect is approximately 3 days, with peak effects occurring within 2 to 6 weeks. Of the tricyclic antidepressants, amitriptyline is the gold standard of analgesic antidepressants. Of the newest serotonin specific reuptake inhibitors (SSRIs), only paroxetine appears to have analgesic effects in a neuropathic pain model, although other SSRIs may be helpful in headache and back pain. Patients should be counseled when antidepressants are initiated that a serial trial of a variety of drugs may be necessary to determine which is the most effective. Greater caution is required when these drugs are used in patients with HIV dementia or other CNS complications, cardiac arrhythmias, or hepatic dysfunction.

The anticonvulsants, including carbamazepine, valproic acid, phenytoin, gabapentin, and clonazepam, are first-line therapy for electric, shooting, and intermittent neuropathic pain. These drugs are also used for neuropathic pain that is refractory to antidepressants. Their potential adverse effects necessitate close clinical and laboratory monitoring, including serum drug levels.

In addition, mexiletine blocks sodium and potassium channels and may play a role in treating refractory neuropathic pain. Corticosteroids stabilize neuronal membranes and reduce the swelling around tumors. The short-term use of corticosteroids may increase patients' appetite and weight gain and improve their mood, but side effects of these drugs prohibit their long-term use.
Adjuvant Drugs to Counteract Opioid Side Effects

An additional category of different types of adjuvant drugs includes laxatives, antiemetics, antihistamines, psychostimulants to counteract sedation, and neurotics to counteract hallucinations.

Undertreatment of Pain in HIV Disease

Pain is significantly undertreated in HIV disease. Dr. Breitbart and his colleagues recently examined the use of analgesics in 550 ambulatory patients with AIDS in New York City. Of 114 patients who reported severe pain (a score of 8 to 10 on the rating scale of 1 to 10) more than 25% were taking no analgesics, 40% were taking an NSAID, and 6% were taking a strong opioid. On the basis of the guidelines in the WHO Analgesic Ladder, a strong or long-acting opioid should be considered in all patients who report pain of this intensity.

Using the pain-management index, a measure for comparing the potency of the analgesics prescribed with the intensity of the pain reported, Breitbart and colleagues were able to compare the pain management used in patients with HIV disease with that used in patients with cancer. According to this pain-management index, only 15% of the 235 patients with HIV disease who reported pain were being given adequate analgesic therapy. The factors that predicted undertreatment in the subset of patients with AIDS were female sex, lower educational levels, injection drug use as a risk factor for HIV infection, greater levels of pain intensity, and patient-related barriers such as being reluctant to complain about pain so as to avoid being labeled a problem patient and to avoid deflecting the focus of treatment from the life-threatening aspects of the disease. Cleeland and colleagues used the same index to evaluate the management of cancer-related pain in 597 patients in Eastern Cooperative Oncology Group studies. In contrast to what Breitbart and colleagues found, 58% of the patients in this analysis were being given adequate analgesic therapy.

Physicians may be reluctant to prescribe opioid drugs for patients with moderate or severe pain for many reasons; some major ones being the physicians' relative lack of knowledge about pain management, lack of ability to assess pain objectively, and fear of contributing to drug abuse or causing readdiction in patients with a history of substance abuse. Not only is the prevalence of HIV-related pain somewhat higher in women, but these women are also twice as likely to be undertreated as are men. Women may have a higher tolerance to pain and may also be more likely to deny the symptom. Problems with communication may complicate effective pain management in children with HIV disease and in patients with HIV-related dementia.

The reluctance of physicians to prescribe opioid medications is a particular obstacle to effective pain management in patients with a history of substance abuse, particularly injection drug use. Patients with a history of injection drug use are the most rapidly growing segment of the population living with HIV disease; the overt and covert issues associated with pain management in this population have to be

<table>
<thead>
<tr>
<th>Table 4. Psychotropic Adjuvant Analgesic Drugs</th>
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<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Imipramine</td>
</tr>
<tr>
<td>Desipramine</td>
</tr>
<tr>
<td>Clomipramine</td>
</tr>
<tr>
<td>Doxepin</td>
</tr>
<tr>
<td>Heterocyclic and noncyclic antidepressants</td>
</tr>
<tr>
<td>Trazodone</td>
</tr>
<tr>
<td>Maprotiline</td>
</tr>
<tr>
<td>Serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Paroxetine</td>
</tr>
<tr>
<td>Sertraline</td>
</tr>
<tr>
<td>Newer agents</td>
</tr>
<tr>
<td>Nefazodone</td>
</tr>
<tr>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Psychostimulants</td>
</tr>
<tr>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
</tr>
<tr>
<td>Pemoline</td>
</tr>
<tr>
<td>Phenothiazines</td>
</tr>
<tr>
<td>Fluphenazine</td>
</tr>
<tr>
<td>Methotrimeprazine</td>
</tr>
<tr>
<td>Butyrophenones</td>
</tr>
<tr>
<td>Haloperidol</td>
</tr>
<tr>
<td>Pimozide</td>
</tr>
<tr>
<td>Antihistamines</td>
</tr>
<tr>
<td>Hydroxyzine</td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Alprazolam</td>
</tr>
<tr>
<td>Clonazepam</td>
</tr>
</tbody>
</table>
addressed. The label “substance abuser” may be misleading; it is important to differentiate between patients who are actively using drugs, those who are in methadone maintenance programs, and those who are in recovery. It is also important to distinguish between drug tolerance, physical dependence, psychological addiction, and drug abuse.

There is a tendency to distrust reports of pain from patients with a history of substance abuse. However, one study by Breitbart and colleagues that compared the experience of pain in 138 patients with a history of injection drug use with that in 112 patients with no history of injection drug use or substance abuse, found no significant differences in pain prevalence, intensity, or relief or pain-related functional interference in the two groups.

The need for pain medication in patients with a history of injection drug use who are in methadone maintenance programs is a separate issue from their need for methadone on a daily basis to prevent drug withdrawal. With a long plasma half-life, 36 to 72 hours, methadone binds to opioid receptors to prevent withdrawal and drug craving. The duration of analgesia in patients given methadone 40 to 100 mg/d is approximately 6 hours. Tolerance to the analgesic effect of opioids develops in patients who have been in methadone maintenance therapy for a long time. Two options for managing pain in patients in methadone maintenance therapy are increasing the daily dose of methadone and giving it on a q6h or a qid basis, or adding a long-acting opioid. Methadone is the less expensive alternative, but access to the drug may be limited.

Pain medications are, in fact, abused. However, clinicians have an obligation to treat pain in all patients and all reports of pain should be accepted and respected. The potential for abuse with opioids may be minimized by establishing clear goals, conditions, limits, and consequences of abuse. Written contracts with certain patients may be useful. It is also important to establish that there will be but one prescriber and to be alert to behaviors that point to drug abuse. A multidimensional approach to pain management that incorporates pharmacologic, psychosocial, and other interventions may also reduce the potential for abuse.

**Clinicians have an obligation to treat pain in all patients and all reports of pain should be accepted and respected.**

**Summary**

Effective pain management improves the quality of life in persons with HIV disease considerably. Yet, despite a great number of effective agents and proven guidelines for using them, pain is significantly undertreated in this population, especially in women and persons with a history of substance abuse. Pain is a complex, subjective, and multidimensional experience; optimal management of pain requires individual treatment plans that address the physical, psychological, and social components of the pain. Nursing organizations and hospices have advanced the practice of pain management in HIV disease, but, among many physicians, a relative lack of information on pain management strategies and a resistance to prescribing opioid drugs remain key clinical obstacles.

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**Suggested Readings**


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a physician to be included in this registry.

What would you consider to be appropriate criteria for inclusion in the registry?

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How many HIV-positive patients are you currently

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