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Perspectives

Reprint

About This Issue

The June issue contains four summaries of talks given at our Boston, Los Angeles, Chicago, and New York continuing medical education courses, all part of the International AIDS Society–USA 2000 Winter/Spring course series, *Improving the Management of* HIV *Disease*: HIV *Pathogenesis*, *Antiretrovirals, and Other Selected Issues in* HIV *Disease Management*.

Two articles, based on presentations by Drs Martin S. Hirsch, Michael S. Saag, and Robert T. Schooley, review current clinical issues around antiretroviral management: the timing and drug selection in initial antiretroviral therapy, and the potential use of new investigational drugs. Also included are articles on care for specific patient populations. Dr Gerald H. Friedland examined "triple-diagnosed" patients with HIV infection, mental illness, and substance abuse, and Dr Donna C. Futterman reviewed the status of HIV in adolescents.

This issue contains a reprint of updated recommendations on antiretroviral drug resistance testing made by an International AIDS Society–USA panel, published in the May 10, 2000, issue of the *Journal of the American Medical Association*. These recommendations are published in the context of a rapidly increasing body of data on the resistance profiles of currently available drugs, data on the clinical utility of drug resistance testing, and the availability of assays to assess drug resistance.

Please also refer to page 18 for a profile of our audience—HIV and AIDS care practitioners who attend International AIDS Society–USA continuing medical education courses. Culled from a survey conducted at four courses in 1999, the data show the general characteristics and educational needs and habits of the survey participants and examine their views on who should provide care for individuals with HIV and AIDS.

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Perspectives

Reprint

Announcements

Perspectives

Investigational Drugs in HIV Therapy: Review of Select New Antiretrovirals

Martin S. Hirsch, MD

New antiretroviral drugs at various stages of investigation and development were reviewed by Martin S. Hirsch, MD, at the Boston course in March.

Optimal HIV-1 suppression often is difficult to achieve and maintain with currently available antiretroviral drugs, and viral resistance eventually emerges to many drugs. Chronic antiretroviral therapy is also associated with complications such as body fat redistribution, hypertriglyceridemia and hypercholesterolemia, abnormal glucose metabolism, lactic acidosis, pancreatitis, avascular necrosis of bone, and osteoporosis. New drugs are needed to enhance anti-HIV potency, overcome viral resistance, increase tolerability and convenience, and reduce toxicity. A number of antiretroviral drugs are in development, including new nucleotide reverse transcriptase inhibitors (*nt*RTIs), nucleoside reverse transcriptase inhibitors (nRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, fusion and coreceptor inhibitors, and integrase inhibitors. This selective review will summarize some of the more promising compounds under study.

Nucleotide Reverse Transcriptase Inhibitors

Tenofovir

Tenofovir disoproxil fumarate is an investigational analogue of dAMP that does not require initial phosphorylation by viral kinases. Its predecessor adefovir is no longer being developed for HIV therapy because of concerns related to antiviral activity and renal toxicity. Tenofovir exhibits a half-life that permits once-daily dosing and has potent in vitro activity against HIV (and simian immunodeficiency virus [SIV]), including activity against nRTI-resistant HIV and multidrug-resistant virus with the Q151M mutation.

In a short-term clinical study, tenofovir produced a clear dose-response in viral load reduction. Although viral load decreased by approximately 1.5 log in treatment-naive patients, the decrease was smaller in treatment-experienced patients. In a subsequent study, treatment-experienced patients with at least 8 weeks of stable potent therapy (mean, 4.6 years of therapy), viral load of 400 to 100,000 HIV RNA copies/mL, and adequate renal function had tenofovir at 75, 150, or 300 mg or placebo added to their current regimen. In this study, 85% of patients had zidovudine-resistant virus, most with multiple mutations, and 67% had the lamivudine-associated M184V resistance mutation. As shown in Figure 1, dose-related decreases in viral load were observed, with a maximum decrease of approximately 0.8 log with the highest dose. A similar response was observed in the initial placebo group when tenofovir was added at 24 weeks.

Resistance to tenofovir can be generated in vitro by a K65R mutation, but thus far this mutation appears to be uncommon in tenofovir-treated patients. The insertion mutations at positions 69 and 70 of RT that are associated with multi-nRTI resistance confer cross-resistance to tenofovir. Although available clinical data on tenofovir use thus far extend only to the 24- to 72-week period, significant nephrotoxicity has not been observed to date; adefovir-associated nephrotoxicity was commonly observed within this time frame. Phase III trials of tenofovir are in progress. A limited expanded access program has been conducted for patients with advanced disease, but is no longer open to enrollment.

Nucleoside Reverse Transcriptase Inhibitors

Emtricitabine

Emtricitabine (FTC) is a highly active oxathiolane nucleoside analogue with potency against HIV and hepatitis B virus (HBV) in vitro. Its structure differs from that of lamivudine only in the presence of a fluoride residue at position 5 on the pyrimidine ring. Emtricitabine is 4- to 10-times more potent than lamivudine in vitro (in some systems) and is synergistic with a broad range of nRTIs, NNRTIs, and

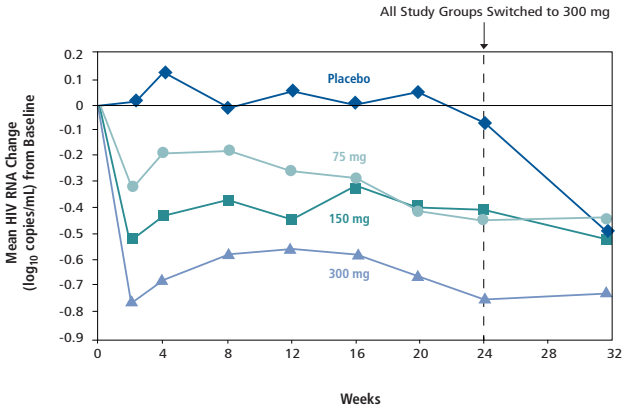

Figure **1.** Mean change in plasma viral load according to tenofovir dose group in study 902 in treatment-experienced patients. Courtesy of Ian McGowan, MD, PhD, Gilead Sciences, Foster City, Calif.

Dr Hirsch is Professor of Medicine at Harvard Medical School and Director of Clinical AIDS Research at the Massachusetts General Hospital in Boston. Dr Hirsch is also a member of the International AIDS Society–USA Antiretroviral Therapy Guidelines Panel and the chair of the organization's panel on guidelines for the clinical use of resistance testing in antiretroviral management.

protease inhibitors. Plasma and intracellular pharmacokinetics support once-daily dosing of the drug, with high intracellular levels of the triphosphate form being dose-related (apparent saturation at doses >200 mg). In early clinical studies, administration of doses of 200 mg or higher was associated with 1.72- to 1.92-log decreases in viral load. Clinical studies assessing once-daily dosing are under way.

DAPD

Diaminopurine dioxolane (DAPD), which is converted in vivo to the dioxolane guanine analogue DXG, also exhibits activity against HIV and HBV. The pharmacokinetics of the drug support once- or twice-daily dosing. DAPD retains activity against zidovudine- and lamivudine-resistant mutants, and is active against some virus with codon 69 mutations conferring multi-nRTI resistance. Virus with the K103N mutation associated with NNRTI resistance may exhibit hypersensitivity to DAPD. Resistance to DAPD is selected in vitro by K65R and L74V mutations. Once-daily and twice-daily dose schedules currently are being assessed in Phase I/II studies. Marked short-term activity has been observed in treatment-naive patients, with 14-day data indicating viral load decreases of 1.5 to 2 log; treatment-experienced patients currently are being enrolled in the early phase studies.

Nonnucleoside Reverse Transcriptase Inhibitors

Capravirine

Capravirine (Ag1549) retains activity in vitro against virus with some of the single-point mutations characteristic of NNRTI resistance, including the K103N mutation associated with resistance to currently approved NNRTIs. It also exhibits activity, albeit reduced, against some HIV isolates with more than one NNRTI resistance mutation. High-level resistance to the drug requires more than one mutation; concomitant V106A and F227L mutations are associated with a more than 380-fold increase in 50% inhibitory concentration (IC_{50}). In testing of doses of up to 2100 mg twice daily in NNRTI-naive patients, viral load was reduced by 1.7 log over 10 to 28 days, with minimal toxicity (primarily diarrhea and nausea) being observed. Coadministration with nelfinavir results in a 5-fold increase in the minimum concentration of capravirine. Phase II and III studies of capravirine have been initiated.

Protease Inhibitors

Lopinavir

Lopinavir (ABT-378/r) is a combination of ritonavir and ABT-378, an investigational protease inhibitor structurally related to ritonavir. ABT-378 exhibits 10-fold greater in vitro activity against HIV and retains activity against HIV with the codon 82 mutation characteristic of initial resistance to ritonavir and indinavir. It is also more active than ritonavir against virus with numerous ritonavir resistance mutations. Each tablet of lopinavir contains 133.3 mg of ABT-378 and 33.3 mg of ritonavir. Plasma levels of ABT-378 are dramatically increased by coadministration of low doses of ritonavir, permitting twice-daily dosing.

Lopinavir has been assessed in treatment-naive and treatment-experienced patients. In the M97-720 study, 100 treatment-naive patients received ABT-378/r 200/100 mg (respectively) or 400/100 mg twice daily alone for 3 weeks. This was followed by the addition of stavudine/lamivudine (Group 1) or ABT-378/r (400/100 mg or 400/200 mg bid) together with stavudine/lamivudine from study day 1 (Group 2). All patients converted to open-label lopinavir 400/100 mg twice daily plus the other 2 drugs at week 48. More than 90% of patients had viral load decreases to below 400 copies/mL at 72 weeks in on-treatment analysis. The most common adverse events were diarrhea (19% and 22% in Groups 1 and 2, respectively), nausea (6% and 19%), and abnormal stools (19% and 3%). Elevations of total cholesterol or triglyceride levels were observed in 12% to 15% of patients respectively in the 2 groups.

In Study M97-765, 70 patients who had been receiving a protease inhibitor and 2 nRTIs for at least 3 months and had single protease inhibitor failure with viral loads of 1000 to 100,000 copies/mL received ABT-378/r 400/100 mg or 400/200 mg twice daily. Nevirapine was added and the nRTIs were changed to include at least 1 new drug at day 15. Viral load was reduced to below 400 copies/mL in 84% of patients at week 24 in on-treatment analysis. The mean increase in CD4+ cell count was 125/μL at week 48. This degree of activity in treatment-experienced patients appears to be related to the ability of this combination at either study dose to maintain plasma ABT-378 concentrations exceeding the 50% effective concentration (EC_{50}) for virus in these patients (Figure 2). Lopinavir currently is being evaluated in a Phase II study in patients with multiple protease inhibitor experience.

Phase III pivotal studies of lopinavir are under way. It currently is also available in an expanded access program limited to patients with advanced HIV disease, and criteria for wider availability are in development.

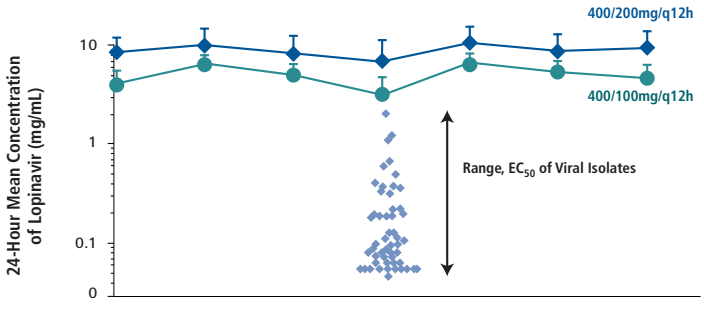

Figure **2.** Lopinavir 24-hour mean concentrations at study dosages and 50% effective concentrations (EC_{50}) for HIV isolates (adjusted for 50% serum) in study M97-765. Courtesy of Eugene Sun, Abbott Laboratories, Abbott Park, Ill.

Tipranavir

Tipranavir is a nonpeptide drug that exhibits broad activity against protease inhibitor-resistant variants. A study of 107 highly protease inhibitor-resistant clinical virus variants (>10-fold reduction in susceptibility to 3 or more drugs) showed that 90% were susceptible to tipranavir. Some variants were hypersensitive to the drug and only 3% had more than 10-fold reduction in susceptibility. In vitro resistance to tipranavir is associated with the 82T/84V

Table 1. Early Phase Study of a Pentafuside-Containing Multidrug Salvage Regimen

Patients/ Drug History	55 patients/Used a median of 11 prior antiretrovirals (93% with exposure to 3 drug classes)
Median Baseline CD4+ Count	70 cells/mL
Median Baseline HIV RNA	4.9 $\log_{10}$ copies/mL
At 16 weeks, no. of patients with:	
HIV RNA >1 $\log_{10}$ below baseline or with <400 copies/mL at 16 weeks	33 of 55 (60%)
<400 copies/mL	20 of 55 (36%)

Adapted from Lalezari et al, 39th ICAAC, 1999.

and 84V/90M mutations, but these mutations have not been consistently observed.

Development of tipranavir has been hindered by formulation problems and rapid metabolism by the cytochrome P450 3A4 isoenzyme. Initial studies indicated that the drug was associated with a modest 1.0- to 1.5-log decrease in viral load over 28 days with 1500 mg 3 times a day; it appears that adherence to the study regimen was poor due to the number of pills required. A new formulation currently is being evaluated, and it has been shown that trough concentrations of the drug are increased 7- to 40-fold by coadministered ritonavir, allowing twice-daily dosing of the drug. Phase II studies of the new formulation of tipranavir combined with ritonavir (1200/200 mg bid, respectively) in treatment-naive patients are in progress.

BMS 232,632

BMS 232,632 is an azapeptide drug with activity against variants resistant to nelfinavir and saquinavir and partial activity against indinavir- and ritonavir-resistant virus. It is suspected to have a resistance pathway unique among protease inhibitors. Bioavailability of the drug is 53% to 72% and the terminal half-life is 3 to 7 hours, suggesting that once-daily dosing may provide adequate minimum concentrations. The drug also exhibits favorable pharmacokinetics in combination with saquinavir. Phase II studies of BMS 232,632 are in progress, including evaluation of short-term activity of once-daily monotherapy and longer-term activity of combinations with 2 nRTIs in treatment-naive patients and of once-daily administration in combination with saquinavir in protease inhibitor-experienced patients.

Fusion Inhibitors

Pentafuside

Pentafuside (T-20), a 36-amino acid peptide, is a specific and potent inhibitor of gp41-mediated fusion of HIV with the host cell membrane. It does not exhibit cross-resistance to other current antiretrovirals and has a synergistic effect in vitro with several reverse transcriptase inhibitors and protease inhibitors. The drug must be administered parenterally and is currently being evaluated using a twice-daily subcutaneous injection regimen. In an early-phase study, pentafuside treatment was associated with a 1.5- to 2.0-log decrease in viral load and a mean increase in CD4+ cell count of 215/µL over 32 weeks in treatment-experienced patients. Sixteen-week data are presented in Table 1. Systemic toxicity with the drug has been infrequent. Resistant isolates have been obtained in vitro and resistance in vivo has been observed after prolonged therapy in association with mutations in HIV gp41. Pentafuside currently is in Phase II trials.

T-1249

T-1249, a 39-amino acid hybrid peptide of HIV-1, HIV-2, and SIV, was designed to bind to a different gp41 region than pentafuside. It is 2- to 100-times more active in vitro than pentafuside and is highly active against pentafuside-resistant HIV. The drug was designed to provide improved pharmacokinetics, and Phase I/II dose-escalating trials including once-daily parenteral administration are under way.

Although pentafuside and T-1249 may prove to be of clinical utility, the need for long-term subcutaneous administration is a drawback. Orally available fusion inhibitors directed at the same target are under development.

Drugs Acting on Other Targets

Coreceptor Blockers

Other drugs in development that act at the viral attachment or entry stage include blockers of the HIV coreceptors CCR5 (AOP-RANTES and Schering-C) and CXCR4 (AMD3100 and T140). Studies in vitro have shown that the combination of pentafuside and the CXCR4 blocker AMD3100 is strongly synergistic against lymphotropic (X4) viral isolates, indicating that targeting of sequential steps in attachment or entry may be a useful strategy. Clinical activity of coreceptor blocker compounds has yet to be demonstrated.

Integrase Inhibitors

The HIV integrase is responsible for inserting proviral DNA into the host cell genome. This enzyme, for which there is no known cellular homologue, is conserved in all retroviruses and is required for stable maintenance of the viral genome and efficient viral gene expression. Much work has been done over the past several years in the attempt to develop integrase inhibitors. Progress has been slowed by the difficulty inherent in the in vitro study of the multistep process culminating in integration of the proviral DNA. Inhibitor molecules identified in this research have been primarily DNA-binding compounds that prevent assembly of the viral preintegration complex. These inhibitors are relatively nonspecific for HIV integrase and exhibit poor antiretroviral activity in tissue culture.

However, a recent report indicates the development of a class of integrase inhibitors that bind to the preintegration complex and inhibit the strand-transfer reaction in integration. These molecules exhibit potent inhibition of HIV replication in tissue culture; their activity against HIV integrase is indicated by the development of resistance mutations mapping to the integrase *int* region of the HIV *pol* gene with

serial passage of virus in the presence of the inhibitors. Candidate molecules in this class currently are undergoing modification to generate clinically useful compounds.

Suggested Reading

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Perspectives

Initiation of Antiretroviral Therapy: Current Controversies in When and with What to Start

Initiation of antiretroviral therapy was discussed at the Los Angeles and Chicago courses in February and April by Michael S. Saag, MD, and Robert T. Schooley, MD, with the purpose of presenting the relative merits and risks of earlier initiation and deferred initiation as well as the different types of regimens appropriate for initial therapy. Dr Saag presented the rationale for deferring initiation and Dr Schooley presented the rationale for early initiation.

Initial Therapy: Treat Later, Keep Options Open

Michael S. Saag, MD

Rationale for Later Initiation

The goals of antiretroviral therapy can be seen as 2-fold: to prevent clinical progression and to prevent or delay development of resistance. The current dilemma in the initiation of treatment stems from considerations pertaining to these goals. Dr Saag noted that to prevent the emergence of viral resistance, relatively complete viral suppression is required. However, less than maximal suppression of viral load throughout therapy can still confer a beneficial effect. A sustained reduction of 0.5 log HIV RNA copies/mL below baseline is associated with relative maintenance of CD4+ cell count over 3 years (Deeks et al, 7th CROI, 2000).

The "treat early, treat hard" approach to therapy was initially linked with the idea that complete and maintained viral suppression could result in the eradication of HIV from the body over a relatively short (eg, 3-year) treatment course. With this approach, the first treatment is envisioned as the opportunity to take the "best shot" at achieving profound suppression of viral replication, and hopefully, eradication. Based on current knowledge of HIV pathogenesis, early and profound suppression could be expected to prevent development of resistance by limiting replication, preserving immune system integrity, and creating a higher virologic hurdle for emergence of viral resistance.

Although many aspects of this rationale remain sound, the approach also rests on assumptions concerning adherence, toxicity, pharmacokinetics, immune reconstitution, and antiretroviral effect that have proven either difficult to realize or unsupported.

- Complete adherence to complex antiretroviral regimens is difficult to maintain.
- Although serious toxicity occurs infrequently with initial treatment in early disease, prolonged treatment is associated with a number of disturbing complications.
- Drug pharmacokinetics and pharmacodynamics are subject to variability that can reduce effectiveness of treatment.
- It was believed that effective treatment initiated later in the course of disease would not be accompanied by any meaningful immune reconstitution. However, treatment initiated at relatively low CD4+ cell counts (eg, 350/µL) can be accompanied by immune restoration that does not seem to be clinically distinguishable from immune function at a relatively higher cell count (eg, 600/µL).
- Achieving HIV RNA levels below assay detection is associated with residual viral replication. Studies correlating the number of viral RNA-positive lymph node cells with plasma viral RNA level show that plasma RNA levels of 50 copies/mL may be associated with the presence of approximately 250,000 cells that are actively producing virus. Ongoing replication in these cells is reflected by evolution in the sequence of HIV envelope in virus from patients with suppression to below 50 copies/mL for up to 24 months. Other studies have shown that the half-life of latently infected cells, which were initially thought to survive for 14 to 21 days under potent antiretroviral drug pressure, is at least 6 months and perhaps as long as 44 months, with the latter estimate indicating that complete suppression for approximately 60 years would be required for viral eradication. This long period and apparent half-life likely reflects the ongoing generation of latently infected cells.

> The "treat early, treat hard" approach was initially linked with the idea that eradication could be achieved in a relatively short time

There are additional considerations that argue against universal application of very early treatment aimed at maximal suppression, including the failure of potent antiretroviral therapy to achieve HIV RNA levels below the limits of detection in a substantial proportion of patients, and the limitations of subsequent treatment options in patients in whom treatment is failing. In addition to the data regarding the relative stability of CD4+ counts in patients with maintained, relatively small reductions (0.5 to 1.01 log) in viral load, data on progression of HIV disease in untreated individuals from the Multicenter AIDS Cohort Study (MACS)

Dr Saag is Professor of Medicine and Director of the AIDS Outpatient Clinic at The University of Alabama at Birmingham. Dr Schooley is Tim Gill Professor of Medicine and Head of the Division of Infectious Diseases at the University of Colorado Health Sciences Center in Denver.

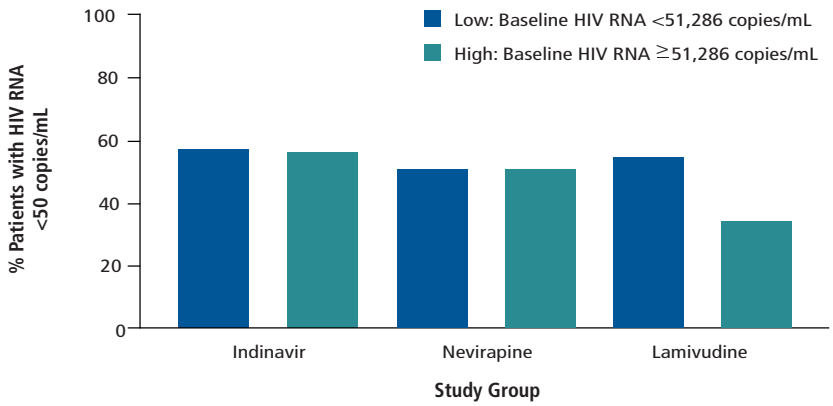

Figure **1.** Proportion of patients receiving dual nRTIs plus indinavir, nevirapine, or lamivudine with viral load below limits of detection (50 copies/mL) by baseline viral load at 48 weeks in an intent-to-treat analysis of the Atlantic study. Courtesy of Robert L. Murphy, MD.

indicate that the rate of natural progression is quite low among individuals with, for example, CD4+ cell counts of 500/µL to 750/µL and viral loads of 3000 to 10,000 copies/mL. With effective treatment, delay of progression could be expected to be markedly increased in such individuals.

Based on such considerations, a more conservative approach to treatment has become increasingly attractive. Treatment may be initiated relatively early rather than very early (eg, at CD4+ cell counts of 350/µL to 500/µL) using potent combinations intended to reduce viral load below 50 copies/mL. The selection of the specific regimen should be based on the likelihood of patient tolerance and adherence, with consideration of short-term and long-term toxicities. Initial treatment should also be selected with the aim of keeping options for subsequent treatment open, and eventual failure of the regimen should be anticipated. Most importantly, patients should understand and accept the rationale for treatment and be "ready to start" therapy.

Strategies for keeping subsequent treatment options available require consideration of which drugs could be used after the initial combination, based on what is known about class cross-resistance. Virologic failure on a particular regimen may not be associated with development of resistance to all of the drugs in the regimen—eg, as has been found for protease inhibitor and dual nucleoside reverse transcriptase inhibitor (nRTI) regimens containing lamivudine, in which lamivudine may be the only drug associated with resistance in the regimen. Regimens including a protease inhibitor, a nonnucleoside reverse transcriptase inhibitor (NNRTI), and an nRTI are probably best avoided as initial treatment, since their use may result in few subsequent options. Regimens for initial treatment may be selected based on patient risk; for example, for patients with a relatively low viral load, triple nRTI therapy or dual nRTI/NNRTI treatment may be used. For patients with advanced disease, a 4-drug combination including 2 protease inhibitors, one of which (eg, ritonavir) is a pharmacokinetic enhancer of the other, may be optimal. Potential advantages of a protease inhibitor/dual nRTI regimen include the fact that it has the longest experience for viral suppression; disadvantages include its complexity and high pill burden, potential long-term toxicity, risk of suboptimal drug levels associated with high interindividual pharmacokinetic variability, and potential compromise of future protease inhibitor regimens. Potential advantages of a regimen combining an NNRTI and 2 nRTIs include deferral of use of a protease inhibitor and a relatively low pill burden; disadvantages include the limited long-term data on use of such regimens and the potential compromise of future use of NNRTIs.

Protease Inhibitor-Sparing Initial Regimens

Interest in protease inhibitor-sparing regimens as initial therapy has increased with reports of longer-term complications that have been associated to some degree with this class of drugs, and with the desire to reserve the class for subsequent therapy. The Atlantic study evaluated dual nRTI regimens combined with indinavir, nevirapine, or lamivudine (Murphy et al, 39th ICAAC, 1999). Comparable activity was observed in all 3 groups among patients with relatively low baseline viral load (<50,000 copies/mL). However, as shown in Figure 1, 48-week data from an intent-to-treat analysis indicate that the triple nRTI combination performed less well in reducing plasma viral load to levels below detection in patients with baseline viral load above 50,000 copies/mL, and the nevirapine-containing combination was comparable to that including the protease inhibitor at both lower and higher baseline viral loads. Reduced effectiveness at higher baseline viral loads is a limitation of some antiretroviral regimens. An analysis of trials using potent regimens containing indinavir, nelfinavir, nevirapine, or efavirenz showed a general trend for reduced effectiveness in lowering viral load to below 500 copies/mL in patients with higher baseline viral load.

A common question concerns the relative potency of different NNRTI-containing regimens. An analysis of studies using nevirapine-containing regimens in patients with higher viral load levels showed data similar to that in the previously mentioned study. However, the relative potencies of efavirenz- and nevirapine-containing initial regimens will be clarified in directly comparative trials, which are ongoing.

Analysis of available comparative and noncomparative data on initial potent regimens suggests comparable effects among protease inhibitor-including and protease inhibitor-sparing regimens. In a study by Staszewski and colleagues (NEJM, 1999), efavirenz/lamivudine/zidovudine was at least equal to indinavir/lamivudine/zidovudine in virologic and immunologic effects at 48 weeks; similar comparability of outcomes was reported in a trial by Katlama and colleagues assessing nevirapine/didanosine/stavudine versus indinavir/didanosine/stavudine.

A recently reported meta-analysis included intent-to-treat results of trials of triple-drug antiretroviral therapy (defined as dual nRTI plus protease inhibitor, NNRTI, or nRTI regimens) in groups of 30 or more patients with 2 or more weeks of prior drug exposure who were treated for at least 24 weeks (Bartlett et al, 7th CROI, 2000). Analysis of 48-week results indicate comparable effectiveness among the regimens in reducing viral load to levels below 400 copies/mL or to below 50 copies/mL and comparable degrees of increase in CD4+ cell count. These findings suggest

that protease inhibitor-sparing regimens (ie, an NNRTI and 2 nRTIs) may be used in initial treatment without apparent reduction in potency. Multivariate linear regression analysis indicated that among variables including drug class, baseline CD4+ cell count, and baseline viral load, only pill count was significantly predictive of reduction of viral load to 400 copies/mL or less or 50 copies/mL or less and increases in CD4+ cell count.

Conclusions

Potent antiretroviral therapy has had a profound impact on HIV disease mortality. However, eradication is still not achievable with current regimens, the incidence of virologic failure on potent therapy increases with duration of use of the regimen, and long-term toxicities are proving to be common. The consequences of failure of potent therapy on mortality are uncertain, but ominous. It thus appears that a reasonable approach to treatment, given the considerations discussed above, is to remember that antiretroviral therapy is an undertaking comparable to a marathon rather than a sprint, and that patients may best be served by later treatment initiation and the preservation of subsequent treatment options.

Initial Therapy: Risks and Benefits of Earlier Initiation of Antiretroviral Therapy

Robert T. Schooley, MD

The rationale for early initiation of antiretroviral treatment is based on several issues as described below.

Immunologic Damage Is Progressive and Only Partially Reversible

HIV disease progression is driven by the massive production of virions primarily in activated CD4+ cells, with CD4+ cell depletion outstripping the ability of the immune system to replenish lost cells. Although cohort data on natural history progression to AIDS according to viral load and CD4+ cell count provide an idea of risk of progression over defined periods of time in the infected population, individual risk of progression can vary according to a number of host and viral factors. Further, it remains impossible to determine in common clinical practice if a patient has undergone immunologic damage that results in gaps in his or her immune repertoire that will not be restored when viral replication is suppressed. Data from ACTG 375 indicate that although patients exhibited average CD4+ cell increases of approximately 150/µL, the breadth of immune response indicated by CD4+ cell diversity is restricted compared with that in individuals without HIV infection. The occurrence of opportunistic conditions at relatively elevated CD4+ cell counts in some patients under antiretroviral therapy suggests that some patients do have holes in the CD4+ cell repertoire that persist despite therapy-related increases in CD4+ cell count.

Earlier Intervention Is Associated with Greater Likelihood of Virologic Success

Perhaps the most compelling reason for early initiation of therapy is that likelihood of virologic response predictive of durable response decreases with decreasing CD4+ cell counts and increasing baseline plasma HIV RNA levels. Data from the Swiss HIV Cohort Study, for example, indicate that each 1-log increase in plasma viral load at baseline was associated with a 25% reduction in likelihood of achieving viral load of less than 400 copies/mL (relative hazard, 0.75; $P<0.0001$) and that each 100/µL increase in CD4+ cell count was associated with a relative hazard of 1.04 ($P<0.0001$) for achieving this degree of viral suppression.

A similar conclusion emerges from analysis of data from a series of studies assessing the use of indinavir/zidovudine/lamivudine in different patient populations: patients with CD4+ cell counts of 50/µL or below, any viral load, and 6 or more months of prior zidovudine but no prior lamivudine or protease inhibitor treatment (Merck Study 039); patients with CD4+ cell counts of 50/µL to 400/µL, viral load of 20,000 or more copies/mL, and 6 or more months of prior zidovudine but no lamivudine or protease inhibitor experience (Merck Study 035); and treatment-naive patients with CD4+ cell counts of 500/µL and above and viral load of 1000 copies/mL or more (Merck Study 060).

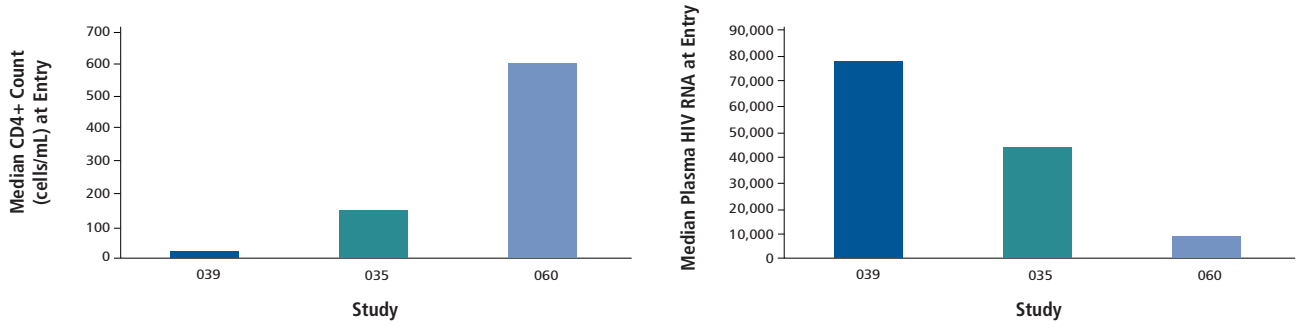

Figure **2.** Median CD4+ cell counts (left) and plasma HIV RNA levels (right) in Merck studies 039, 035, and 060. Courtesy of Michael N. Robertson, MD, and Anne R. Meibohm, PhD, Merck & Co, Inc, West Point, Pa.

Median viral load levels in patients in these 3 studies were highest in the Study 039 patients and lowest in the Study 060 patients (Figure 2). The proportion of patients achieving viral load of less than 50 copies/mL on therapy was greatest in Study 060 (ie, those with the highest initial CD4+ cell counts and lowest initial viral loads), intermediate in study 035, and lowest in study 039, with the proportions remaining fairly constant over time (Figure 3). The fact that patients in the 035 and 039 studies had prior zidovudine experience should be taken into account in interpreting these findings; however, the results of the analysis suggest that treatment at higher CD4+ cell count and lower viral load is more frequently associated with initial and durable virologic response.

Suppression of viral load to as low a level as possible is important in preserving response to antiretroviral drugs (Meibohm et al, 7th CROI, 2000). Rates of decay of virus in latent reservoirs may depend on the patient population studied; patients exhibiting no or slower decline may be those in whom reseeding of the reservoir occurs as a result of lack of adherence to the antiretroviral regimen. In addition, although the relatively slow viral genetic evolution that has been described in patients with viral load below limits of detection has not yet been associated with loss of virologic control, it seems likely that such evolution will eventually result in emergence of resistant virus. The emergence of resistant virus would appear to be likely to occur more rapidly if ongoing replication at higher viral load levels is permitted.

New Therapeutics Are in Development

There is appropriate concern regarding limitation of subsequent treatment options in patients failing initial regimens with currently available drugs. However, new agents are in development to supplement the large number of available drugs. These include drugs with reduced within-class cross-resistance, such as the protease inhibitor combination lopinavir (ABT-378/ritonavir), the nucleotide reverse transcriptase inhibitor tenofovir, and the nRTI DAPD, as well as drugs that target other than reverse transcriptase and protease, including pentafuside (T-20) and other fusion inhibitors, chemokine inhibitors, and integrase inhibitors. (See page 4 for a review of selected new investigational drugs.)

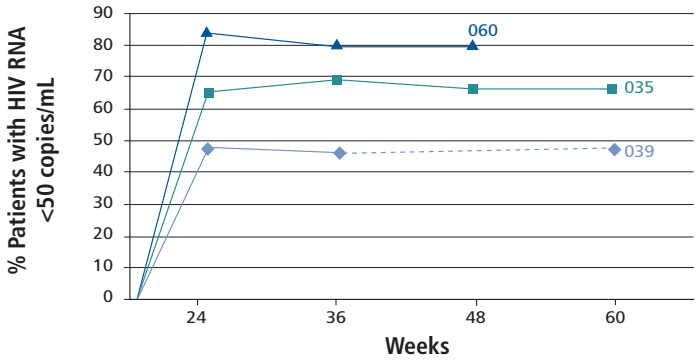

Figure **3.** Proportions of patients with plasma HIV RNA levels less than 50 copies/mL during treatment over time in Merck studies 039, 035, and 060. Courtesy of Michael N. Robertson, MD, and Anne R. Meibohm, PhD, Merck & Co, Inc, West Point, Pa.

Individualization of Drug Selection Based on Viral Genotype and Phenotype Preserves Options

Data from a number of studies have indicated that virologic failure on potent regimens is characterized by sequential drug failure, with regimen failure not implying failure of all drugs in the regimen. For example, in a study of indinavir/zidovudine/lamivudine and indinavir/efavirenz, virologic failure with the first regimen was predominantly characterized by development of the M184V lamivudine resistance mutation, with indinavir resistance mutations being relatively infrequent. Similarly, failure on the indinavir/efavirenz regimen was predominantly associated with the K103N efavirenz resistance mutation.

These and other findings indicate that regimen failure is more likely to be associated with resistance to potent drugs with a lower genetic barrier to resistance (eg, a single mutation permitting high-level resistance) and suggest that individual substitutions for failing drugs may be possible without loss of virologic effect. Individualized drug substitution and regimen intensification are currently being assessed in clinical studies. The increasing awareness that regimen failure is associated with sequential and progressive failure of the components is resulting in an evolution from the paradigm of replacing all drugs in a failing regimen to a paradigm of individualized drug selection based on monitoring for failure of individual components. This approach will permit greater preservation of treatment options, even with currently available antiretroviral drugs.

Magnitude of Toxicities May Be Overestimated and Better Management Approaches Are Likely to Be Developed

Continued study of the long-term toxicities associated with antiretroviral therapy is required to accurately determine the incidence of and mechanisms underlying these effects. The true incidence of protease inhibitor-associated metabolic abnormalities, for example, remains to be defined, with estimates varying among different populations studied using different case definitions over various time periods. The magnitude of cardiovascular risk posed by the lipid abnormalities observed in protease inhibitor recipients is also undefined. Estimates derived from risk in the general population and degree of risk conferred by average low-density lipoprotein and very low-density lipoprotein increases in protease inhibitor recipients indicate that the 10-year risk for a cardiovascular event among 35-year-old nonsmoking, normotensive men is increased from 6.18 cases/100 to 7.59 cases/100 population when the protease inhibitor-associated abnormalities are included. The 10-year risk in 35-year-old male smokers with mild hypertension is increased from 14.5 cases per 100 to 17.1 cases per 100 population when protease inhibitor-associated risk is added. Although the protease inhibitor-associated risk for cardiovascular disease may be important, it needs to be considered in the context of risk associated with withholding of antiretroviral therapy as well as the relative magnitude of cardiovascular risk conferred by traditional cardiovascular risk factors (Grunfeld, 6th CROI, 1999).

Table **1.** International AIDS Society–USA Recommendations for Initiation of Antiretroviral Therapy

	Plasma HIV RNA Level (copies/mL)		
CD4+ Count (cells/μL)	**<5000**	**5000-30,000**	**>30,000**
<350	Recommend therapy	Recommend therapy	Recommend therapy
350-500	Consider therapy	Recommend therapy	Recommend therapy
>500	Defer therapy	Consider therapy	Recommend therapy

Adapted from Carpenter et al. *JAMA.* 2000.

It is likely that approaches will be developed to minimize such toxicities as their mechanisms are better understood, including more enlightened drug selection, development of new drugs with less toxic effects, and management addressing the mechanisms underlying the individual effects. Investigation of cofactors in the development of long-term toxicities is under way. In a recently reported animal study, for example, it was found that mice genetically prone to obesity exhibited metabolic abnormalities more frequently than did obesity-resistant mice with exposure to protease inhibitors. Such abnormalities in obesity-resistant mice were increased when the animals were fed a high-fat, high-calorie diet (Lenhard et al, 7th CROI, 2000). Ongoing protocols are examining measures for reversing these metabolic complications.

Conclusions

As shown in Table 1, current recommendations for initiating antiretroviral therapy advocate deferral of therapy for patients with CD4+ cell counts above 500/μL and plasma HIV RNA levels less than 5000 copies/mL. Consideration of therapy is recommended in those with CD4+ cell counts above 500/μL and viral load levels of 5000 to 30,000 copies/mL or those with CD4+ cell counts of 350/μL to 500/μL and viral load levels of more than 5000 copies/mL. Stronger recommendations for initiation are made for all other groups stratified by CD4+ cell count and viral load. Currently, no single answer to the question of when antiretroviral therapy should be started is appropriate for every patient. Factors that need to be considered include CD4+ cell count and viral load, toxicities, and the patient's commitment to treatment. The weight given to these factors in making decisions about initiation is likely to be influenced by advances in the understanding of risks for adverse effects with individual drugs that will alter the risk-to-benefit analysis for individual patients, and by the development of better antiretroviral agents.

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Perspectives

Issues in HIV Therapy in "Triple-Diagnosed" Patients

Gerald H. Friedland, MD

There is great overlap among the population of HIV-1-infected individuals who are active or former drug users and who have serious underlying mental illnesses. Challenges in treating these "triple-diagnosed" patients, particularly with regard to access and adherence to antiretroviral therapy and drug interactions, were discussed at the New York course in March by Gerald H. Friedland, MD.

Epidemiology and Comorbidity

AIDS cases associated with injection drug use account for more than one third of cases in the United States, with recent trends indicating an increase in this proportion. Data from 1997 to 1998 indicate that transmission of HIV related to injection drug use accounts for 24% to 47% of new infections. Heterosexual and perinatal exposure to HIV-infected injection drug users constitutes the major route of HIV transmission. Noninjection drug use also facilitates sexual transmission of HIV infection (eg, through disinhibition) and may be associated with factors that confound treatment of HIV infection, which can be similar to those associated with injection drug use.

The epidemiology of mental illness and HIV infection is not well characterized. However, a number of surveys conducted in the United States and Europe indicate that approximately 20% to 50% of individuals with HIV infection or AIDS have severe mental illness, including personality and mood disorders (major depression; anxiety, panic disorder, or posttraumatic stress disorder; impulsivity or personality disorder; and drug-related disorders), as well as psychoses. Injection drug users with HIV infection have been reported to have a rate of major depression of 26% (5-times that in the general population). Other data indicate that the rate of substance abuse among the population with severe mental illness is 4% to 35% (3 to 25 times that in the general population) and that there is an HIV-seroprevalence rate of at least 2% to 8% in this population (10 to 50 times that in the general population).

Studies using the global assessment of functioning (GAF) instrument, which evaluates personality and social functioning, have indicated that scores for HIV-infected individuals are lower than those for HIV-seronegative injection drug users and fall between those for individuals not in either category and those for individuals hospitalized for psychiatric disease (Figure 1). Other studies among HIV-seropositive and -seronegative drug users who are not in drug treatment programs indicate frequencies of 41% for depression, 10% for suicide attempt, 9% for posttraumatic stress disorder, and 7% for anxiety disorder. Although no difference between HIV-seropositive and HIV-seronegative individuals for specific mental health diagnoses was observed, mental illness was significantly more common in HIV-seropositive individuals overall (39% v 23%, P=0.002).

Antiretroviral Therapy

The complex and intertwined etiologies of HIV disease, substance abuse, and psychiatric disease are associated with biologic, behavioral, clinical, and societal factors that render effective care for the triple-diagnosed patient extremely difficult. Data from the era of potent antiretroviral therapy indicate that there have been marked decreases in rates of opportunistic illness and death in HIV infection by category of HIV transmission. However, the decrease in injection drug users has been smaller than that in other risk behavior categories (Figure 2). Centers for Disease Control and Prevention (CDC) statistics through 1997 indicate that, due to the smaller decrease in mortality in AIDS patients acquiring infection through injection drug use, these patients account for an increasing proportion of deaths in patients with AIDS (>50% in 1997). At the same time, CDC statistics show that the ongoing injection drug use-associated transmission of HIV as well as treatment benefits have resulted in a steady increase in the estimated absolute number of HIV-infected injection drug users in 1997.

Studies performed several years ago and published in 1998 (the ALIVE and Vancouver studies) indicated that only a small minority of infected injection drug users were receiving potent antiretroviral therapy. Factors associated with lack of use of antiretroviral therapy in one study included active drug use, suboptimal health care, not being in a drug treatment program, and recent incarceration. Younger age, female gender, not being in a drug treatment program, and health care

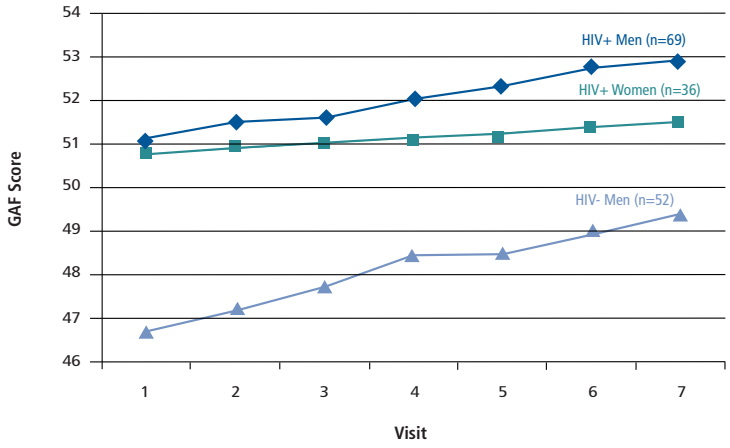

Figure **1.** Mean global assessment of functioning (GAF) score for injection drug users in a longitudinal study according to HIV-seropositive (HIV+) or HIV-seronegative (HIV-) status and male or female gender. Normal scores are approximately 70 or above. Adapted from Rabkin et al, *AIDS,* 1997.

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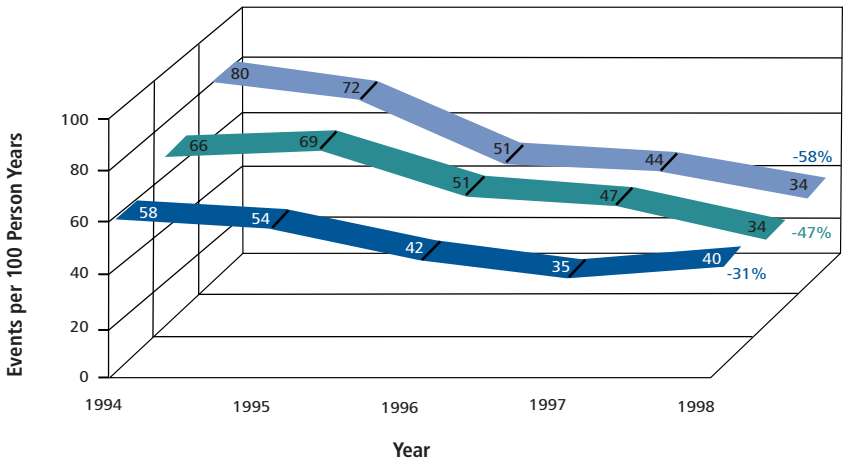

Figure **2.** Rates of opportunistic illness and death (events per 100 patient years) at a Johns Hopkins clinic according to transmission category of injection drug use (light blue), heterosexual contact (green), or male-to-male sexual contact (blue). Overall decrease in rates is shown at right. Adapted from Moore RD et al, *AIDS,* 1999.

provider expertise were associations identified in another study. More recent data from the Johns Hopkins Moore Clinic cohort (Moore et al, AIDS, 1999) indicate that although the rate of use of antiretroviral therapy among active injection drug users was approximately 60% in 1999, it remains lower than rates of use in individuals infected through homosexual or heterosexual contact.

Further, data from the Medicaid population in New York indicate that individuals with drug dependence have significantly reduced adjusted odds for receiving antiretroviral therapy, whereas drug users who are in a drug treatment program have a 40% increased likelihood of using antiretroviral therapy (Turner et al, 7th CR01, 2000). Data on the impact of severe mental illness on the rates of treatment with antiretroviral therapy are not available, although it is well known and documented that depression is a powerful predictor of poor adherence to HIV therapy. Further, having a mental health provider appears, paradoxically, to decrease likelihood of receiving antiretroviral therapy.

Recent studies by investigators at Yale have indicated that trust in the physician is the most important variable influencing acceptance of antiretroviral therapy among injection drug users, with each 1-point increase in score on the Likert scaled "Trust in Physician" instrument being associated with an 8% increase in likelihood of acceptance of antiretroviral therapy. Beliefs about medication also influence HIV therapeutics among drug users. In a recent survey, more than half of substance abuse patients "strongly agreed" or "agreed" that in using antiretroviral therapy, they were being experimented on without being told, that drug companies do not "tell bad things" about their drugs, and that there is a cure for AIDS that the government keeps quiet. Moreover, the majority of patients said they believed that antiretroviral therapy is harmful when taken with heroin, cocaine, or methadone; that they will not take therapy if they are going to get high on "street" drugs; that people "get sick and die" after starting antiretroviral therapy; and that people "get sick and die" after stopping street drugs.

The relative lack of effective drug treatment programs in the United States influences both antiretroviral use and continued transmission of HIV infection among injection drug users. Methadone may be considered one of the most successful chronic disease therapies. Its use is associated with decreased heroin use, improved quality of life, and decreased needle sharing and HIV transmission. It is estimated that only 15% to 20% of individuals eligible for opiate addiction treatment currently are receiving treatment in the United States. This is to be contrasted with countries such as Scotland, where methadone treatment is available through primary care physicians and currently is being received by 40% to 80% of the eligible population. A policy of administering methadone in the primary care setting currently is being reconsidered in the United States.

It is also important to consider broader expertise and availability of mental health treatment in traditional medical settings where patients with HIV disease are seen as well as the converse–provision of HIV expertise and therapy at mental health care sites. Co-location of treatment for all 3 comorbid conditions is the most efficient and likely most successful way of addressing the complex treatment needs of this population.

Drug Interactions

Pharmacokinetic interactions between substance abuse treatments and antiretroviral drugs, as well as drugs used for the treatment of mental illness, can affect efficacy and toxicity of and adherence to treatment for each or all of the comorbid conditions.

Methadone is metabolized by hepatic demethylation and activity of the cytochrome P450 3A4 isoenzyme system and, possibly, other CYP450 isoenzyme systems (1A2, 2C9, 2D6). The methadone derivative LAAM- has similar pharmacokinetics. With regard to pharmacokinetic interactions between methadone and nucleoside reverse transcriptase inhibitors (nRTIs), data from within- and between-subject studies indicate that the zidovudine area under the curve (AUC) concentration is increased by approximately 40% with coadministered methadone, with no change in methadone disposition observed. A crossover study of coadministered methadone and didanosine or stavudine has shown AUC decreases of 60% for didanosine and 18% for stavudine and no change in methadone levels. A recent study indicated that coadministration of abacavir and methadone produced a small but statistically significant increase in clearance (9.9-12.2 L/h), producing a decrease in methadone levels. In addition, a small but significant decrease in maximum abacavir concentration (4.4-2.9 µg/mL) was seen as was a delay in abacavir maximum time concentration (1.5-2.5 h), likely the result of the methadone effect of slowing gastrointestinal motility.

Interactions with methadone may be even more be problematic with the nonnucleoside reverse transcriptase inhibitors (NNRTIs). In a recently reported case series of 7 patients with opiate withdrawal symptoms within 8 days of starting nevirapine, the 3 subjects in whom methadone measurements were obtained had low methadone levels at the onset of symptoms. All of the patients required substantial increases in methadone dose, but only 3 responded to the increase and only

those patients continued to receive nevirapine. A recent report supports the observation of induction of increased metabolism of methadone by nevirapine and extends the findings to efavirenz. In a group of 25 stable-dose methadone patients, measurement of drug levels at baseline and after 2 and 3 weeks showed that the methadone AUC was decreased by 43% in 15 subjects receiving efavirenz and by 46% in 10 receiving nevirapine. Overall, 8 patients had opiate withdrawal symptoms after 8 days and required a mean methadone dose increase of 21.65%. The effect of methadone/ delavirdine coadministration has not been studied; however, based on what is known of delavirdine pharmacokinetics, it is hypothesized that coadministration would result in an increase in methadone levels.

Little is known about the effects of methadone on protease inhibitor pharmacokinetics. Coadministration appears to be associated with some delay in indinavir absorption, but there are yet no published reports on interactions with other protease inhibitors. No effect on methadone levels has been reported with indinavir. Ritonavir, which decreases meperidine levels and increases fentanyl levels, has been reported to decrease methadone levels, although this information is based on use of very low doses of methadone. Nelfinavir has been reported to decrease methadone levels by 30% to 50% without resulting in clinical symptoms. It is hypothesized that nelfinavir may largely affect protein-bound methadone rather than the active free drug. Available preliminary information indicates that saquinavir and amprenavir have minimal effects on methadone level. With regard to therapies for opportunistic infections, most problematic is the long-known rifampin induction of methadone metabolism, with resultant rapid opiate withdrawal. Other clinically significant interactions with opportunistic therapies have not been reported.

There is considerable likelihood of pharmacokinetic interactions between HIV therapies metabolized by the CYP450 system and commonly abused substances. Metabolic pathways of a number of abused substances are shown in Table 1. However, virtually nothing is known of the clinical effects of such interactions. The need for concern is highlighted by a recent case report in which a patient taking the amphetamine methylene dioxymethamphetamine (MDMA) experienced a prolonged amphetamine-like reaction after switching from one protease inhibitor to ritonavir. After taking the nonsedating antihistamine g-hydroxybutyrate (GBH), the patient became comatose.

Table **1.** Metabolic Pathways of Abused Substances

Drug	Metabolic Pathway (CYP Isoenzyme)
Benzodiazepines	
Alprazolam, clorazepate, estazolam, flurazepam, midazolam, triazolam	CYP450 (3A4)
Diazepam	CYP450 (3A4, 2C19)
Lorazepam	Glucuronidation
Opiates	
Buprenorphine, fentanyl, methadone	CYP450 (3A4, 2D6)
Meperidine	CYP450 (3A4?)
Propoxyphene	CYP450 (2D6)
Codeine, hydrocodone, oxycodone	CYP450 (2D6)
Heroin, hydromorphone, morphine	Glucuronidation?
Amphetamines	
Amphetamine, methamphetamine (crystal meth), methylene dioxymethamphetamine (MDMA)	CYP450 (2D6)
Others	
Dronabinol, marijuana, zolpidem	CYP450 (3A4)
Sidenafil	CYP450 (3A4)
Cocaine	Hydrolysis by plasma cholinesterase
g-hydroxybutyrate (GBH)	CYP450

Adapted from Harrington et al. *Arch Intern Med.* 1999.

There is also very little information on potential pharmacokinetic interactions between psychiatric drug therapies and antiretroviral drugs. Although there appears to be minimal to no supporting published literature, it is suspected that interactions occur between protease inhibitors and tricyclics, selective serotonin reuptake inhibitors (metabolized via CYP450 2D6), and bupropion among the antidepressants, and benzodiazepines (metabolized by CYP450 3A4) among the anxiolytics (particularly midazolam and triazolam). No information is available on potential interactions between protease inhibitors and antipsychotics (metabolized via CYP450 1A2, 2D6), nor on potential interactions between NNRTIs or nRTIs and psychiatric drugs. Several recent reports in small numbers of patients demonstrated increases in methadone levels when coadministered with fluvoxamine and sertraline, and less effect with fluoxetine. Although clinical indications for administration of therapies for HIV, substance abuse, and mental illness should be followed, prudence dictates that caution be taken when these drugs are administered concomitantly and that heightened awareness of possible interactions be maintained.

Interactions between antiretrovirals and substance abuse therapies are common, and interactions between antiretrovirals and psychiatric medications may also be common. The most important currently identified interactions are the effect of methadone on nRTIs and the effect of NNRTIs on methadone (and to a lesser extent the effect of protease inhibitors on methadone). Although they are difficult to

perform, pharmacokinetic studies of interactions between HIV therapies and substance abuse and psychiatric medications are essential and clinical studies in this area are urgently needed.

Conclusions

HIV disease, severe mental illness, and substance abuse frequently coexist and complicate and confound treatment efforts. More limited access to care, decreased provision, acceptance, and adherence to therapy, and complex and poorly studied drug interactions all contribute to limiting the benefits of potent antiretroviral therapy in populations with these comorbid conditions. As this population increases, HIV clinicians will need to increase their expertise in the management of comorbid conditions and help develop systems of care that better address the special needs of this population.

There is considerable likelihood of pharmacokinetic interactions between antiretroviral drugs and commonly abused substances

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General Characteristics, Educational Needs, and Expertise of HIV and AIDS Care Providers: Survey Highlights

In the fall of 1999, the International AIDS Society–USA, in collaboration with the UCSF Division of Behavioral Sciences, conducted a survey of attendees at 4 of its advanced continuing medical education (CME) courses, held in New York, Chicago, Los Angeles, and San Francisco. The purpose of the survey was to (1) compile general demographic characteristics of the health care practitioners who provide care to HIV-infected patients, (2) gain a better understanding of this group's educational needs and practices, and (3) explore practitioners' criteria for who should care for HIV-infected patients and their confidence in their own ability to do so.

- Completed surveys were returned by 359 eligible physician course attendees. Of this population, 123 listed their specialty as internal medicine (IM), 109 as infectious diseases (ID), and 85 as family practice or general internal medicine (FP/GIM). The majority were white (69%) men (61%) who worked in an urban setting (77%). The participants were an experienced group: 61% had an HIV-only or HIV-focused practice, and 40% had been involved in HIV care for more than 10 years and 73% for more than 6 years.
- Survey participants reported relying most heavily on regional clinical CME courses (mean, 1.6 on a 4-point scale with "1" being "rely on to a great extent" and "4" being "not at all"), clinical guidelines (1.6), peer-reviewed journals (1.7), and national and international scientific courses (1.7), to guide clinical decision-making.
- The sources of information that participants utilized least often were Internet expert consultations (3.5), Internet audio conferences (3.5), videotapes (3.4), and video conferences (3.4). (Because survey participants were attendees of a regional clinical CME course, selection bias in favor of CME courses is likely.)
- 15% said they used the Internet every day or a few times a week to obtain information on HIV and AIDS care, but 38% said they used the internet less than once a month or not at all for this purpose.

On the subject of who should treat patients with HIV and AIDS, participants expressed the following views:

- 70% of all physicians believed that among medical specialties, the ID specialty best prepares physicians to provide HIV and AIDS care. This figure was highest among participants who were ID specialists themselves (95%) and lowest among FPs/GIMs (48%).
- Physician responses from all specialties surveyed were relatively similar on the question of whether HIV should become a full subspecialty, similar to oncology or infectious diseases; 36% to 46% of physicians in each specialty agreed with the statement.
- Participants across all specialties also agreed that a physician should care for at least 100 patients with HIV/AIDS before he or she is considered an HIV "expert."
- When asked about possible criteria to be used to "certify" HIV expertise, participants ranked HIV CME participation (71% endorsed this item), specific HIV training (63%), and the number of HIV-seropositive patients a practitioner has ever treated or is currently treating (56%) as the most important. Lowest-ranked criteria were passing a test (42%), ID training (33%), and percent of HIV-seropositive patients in patient panel (30%).
- 76% of survey participants would be interested in taking an HIV certification exam if one existed.
- 80% of participants think there should be a professional membership organization for physicians who provide HIV care.

Data gathered from the survey on participants' level of confidence in their ability to provide HIV care are currently being prepared for publication in the scientific literature. Other data from the survey will be used to assess the utility of current and future programs of the International AIDS Society–USA.

We thank the survey participants for their time in completing the survey, which has provided valuable information on practitioners currently providing HIV and AIDS care in the United States.

Perspectives

HIV Infection in Adolescents: Epidemiology and Challenges

Donna C. Futterman, MD

The epidemiology of HIV-1 infection in adolescents and challenges in prevention, testing, and care were discussed at the New York course in March by Donna C. Futterman, MD.

Epidemiology

It is estimated that 1 in 4 people with AIDS in the United States acquired HIV-1 infection in adolescence. Current estimates indicate that 50% of persons with HIV infection worldwide acquire infection by age 25 and that 25% of infections in the United States are acquired before age 22; 17% of US AIDS cases are in persons aged 20 to 29 years. The majority of infected adolescents are unaware of their infection status.

Estimates of the frequency of adolescent HIV infection are largely derived from data on AIDS cases and from our understanding that AIDS develops after approximately 10 years of infection. Data on cumulative AIDS cases reported to the Centers for Disease Control and Prevention (CDC) through 1998 indicate that the number of cases begins to peak in the 25- to 29-year age group (Figure 1). In a study of data from 1994 to 1997, data from 25 states with HIV status reporting systems indicate that the 13- to 24-year age group accounted for 653 cases of AIDS (3% of adult cases) and 7200 cases of HIV infection (14% of adult cases). In states without HIV reporting systems, 10,200 AIDS cases in the 13- to 24-year age group were reported. Use of the ratio of HIV infections to AIDS cases in the reporting states suggests a total number of HIV-infected persons in this age group of approximately 100,000.

Infection occurs disproportionately among the black and Hispanic populations. Data from 1997 indicate that black adolescents accounted for 58% of AIDS cases in the 13- to 19-year age group but represented only 15% of the total US population in this age group. Hispanic adolescents accounted for 25% of AIDS cases but represented 13% of the total population in this age group.

Exposure Categories and Risk Behaviors

CDC data through 1995 indicate that exposure to blood products was the most common form of transmission in AIDS cases in 13- to 19-year-old men (~40%), primarily representing transmission in people with hemophilia (Figure 2). Homosexual sexual contact, however, accounted for more than 35% of cases in this age group and for 60% of cases in the 20- to 24-year age group and by 1996 was the leading transmission category. In a seroprevalence study conducted by the New York Blood Center in 545 men aged 15 to 22 years, who were randomly surveyed at gay hangouts or nightclubs in Greenwich Village in New York City between December 1997 and September 1998, 12% were found by blinded testing to be HIV-infected, with the rates being highest among black men (18%; odds ratio, 9.1). Risk behaviors were very common, with 92% of 545 reporting having anal sex with a man and 30% to 40% reporting unprotected receptive anal intercourse. In total, 67% reported ever having had sex with a woman.

CDC data on AIDS incidence by gender show that whereas women 25 years or older account for approximately one quarter of cases, women account for half of cases in the 13- to 19-year age group (Figure 3). Data through 1996 indicate that heterosexual contact accounts for more than half of AIDS cases in females in the 13- to 19-year age group and slightly less than half in the 20- to 24-year age group (Figure 2).

The behavioral risks among adolescents and young adults are illustrated by a case investigated in upstate New York in December 1997. In this case, a young man with HIV infection had heterosexual contact with dozens of women, many of whom were infected and many of whom also had multiple sexual partners. This type of sexual network involving contact with partners who are not well known is more common among adolescents than supposed. It is conceivable that many such mini-epidemics have occurred and continue to occur in many areas of the country but are masked in urban settings.

Characteristics of sexual transmission of HIV in young persons have been identified with ongoing study. These include a wide variation in the number of partners among those acquiring infection. In most surveys that have been performed, more than half of young women report having had only 1 sexual partner; thus, prevention counseling stressing reduction in number of sexual partners would appear to be inapplicable in many instances. Further, 75% of females are unaware of partner risk. For young men, for whom sex with men is the leading risk behavior, it is clear that orientation does not equal behavior—ie,

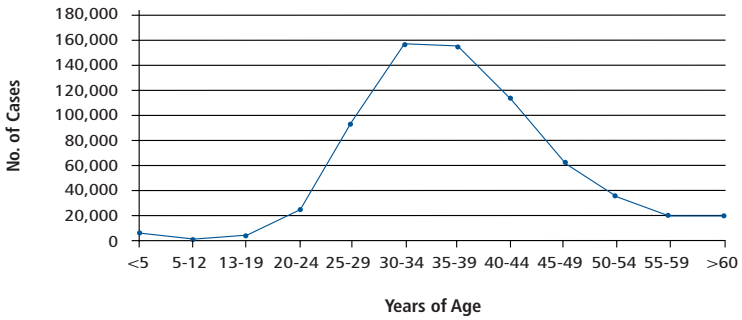

Figure **1.** Cumulative AIDS cases by age reported to the Centers for Disease Control and Prevention through 1998. Adapted from the Centers for Disease Control and Prevention.

Dr Futterman is Associate Professor of Pediatrics at Albert Einstein College of Medicine and Director of the Adolescent AIDS Program at Montefiore Medical Center in Bronx, New York.

that having a "gay identity" is quite different from which sexual behaviors the individual may engage in. In addition, there are high rates of sexual abuse among infected youth, with rates of 25% to 40% having been reported. Further, approximately 20% of infected youth followed in the Montifiore Medical Center Adolescent AIDS Program in the Bronx reported having a parent who is HIV-infected, excluding those who are perinatally infected.

Adolescents are susceptible to acquiring HIV by virtue of a number of factors. Among the behavioral factors is sexual activity; 70% have had sex by the end of high school. Gender power imbalance, particularly between older male and younger female partners, makes it difficult for women to insist on safe sex practices. Biologic factors that put younger women at risk include immaturity of the cervix in adolescence—the single layer of columnar cells is believed to be more vulnerable to transmission than the multiple layers of squamous epithelial cells in the mature cervix. Other sexually transmitted diseases, which facilitate HIV transmission, are frequently asymptomatic in younger women. Male-to-female transmission of virus also appears to be more efficient (although the finding of equivalent transmission efficiency between women and men in developing world settings raises issues regarding the potential biologic explanations for the imbalance). Finally, there are a number of socioeconomic factors that increase susceptibility to HIV infection and other sexually transmitted diseases, including the lack of health care coverage (it is estimated that approximately 25% of teenagers have no coverage), inadequate sex education, and perceived lack of confidentiality in HIV testing and counseling.

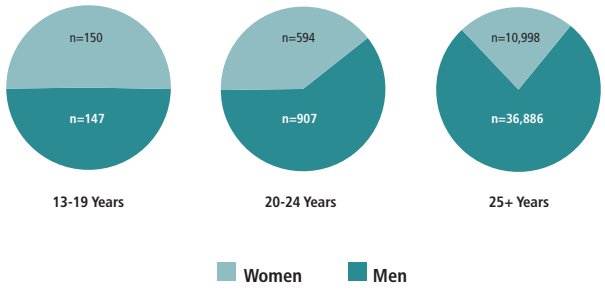

Figure **3.** AIDS incidence by gender in cases reported to the Centers for Disease Control and Prevention in 1998. Adapted from the Centers for Disease Control and Prevention.

Challenges in HIV Care for Adolescents

Among the challenges to be met in addressing HIV infection in adolescents is how to increase risk awareness. It is estimated that one third of individuals currently infected with HIV in this country do not know their infection status and that another third are aware of their infection but are not actively seeking care. These problems are particularly marked among adolescents. New approaches and settings for counseling and testing are needed to increase chances of identifying infected individuals and those at risk. Failure to return for testing results is a major problem in the young age group. Although there is hope that viability of a rapid oral fluid test for HIV infection may enable infection status to be determined at a single visit (the test is currently under investigation), there is also concern that many individuals will then receive only a single counseling session. The ability to perform pretest and posttest counseling at separate visits has been seen as an opportunity for more intensive prevention counseling. Improvements are also needed in linking testing programs to health care. Confidential systems for follow-up have proved to be relatively effective in having adolescents enter and remain in care. Acceptance of and adherence to drug therapy, however, remains a major problem in this age group.

Information on HIV disease progression in adolescents comes from a cohort study conducted by the Adolescent Medicine HIV/AIDS Research Network (AMHARN). These data indicate that there is a high rate of coinfection with other sexually transmitted diseases and that the disease course is similar to that in adults. It was observed, however, that adolescents with hemophilia who acquired infection through infected blood products exhibited a slower course of progression than any other age group. The findings also suggest that adolescents may have more thymic function and thus the potential for immune reconstitution, and therefore may be ideal candidates for early intensive treatment. The impact of puberty on infection course has not yet been defined.

Three major projects in the area of adolescent HIV infection are currently being administered by AMHARN: Project

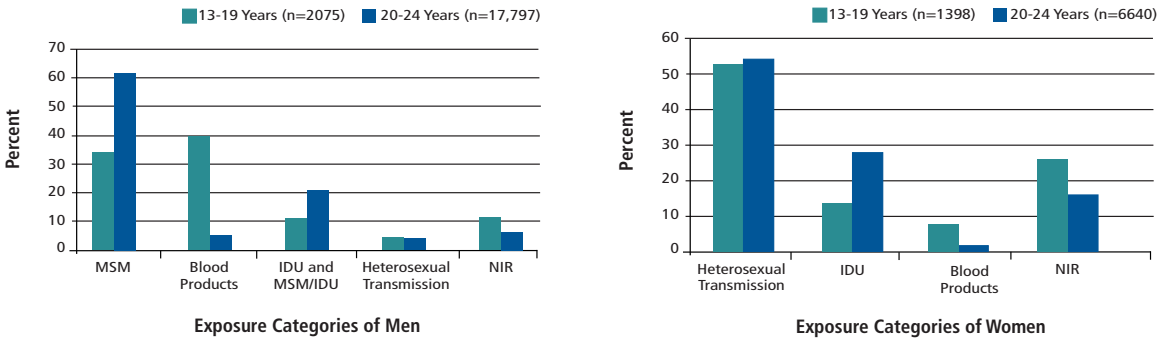

Figure **2.** HIV exposure categories in men (left) and women (right) in 13- to 19- and 20- to 24-year age groups in AIDS cases reported to the Centers for Disease Control and Prevention through 1998. MSM indicates men who have sex with men; IDU indicates injection drug use; NIR indicates no identified risk. Adapted from the Centers for Disease Control and Prevention.

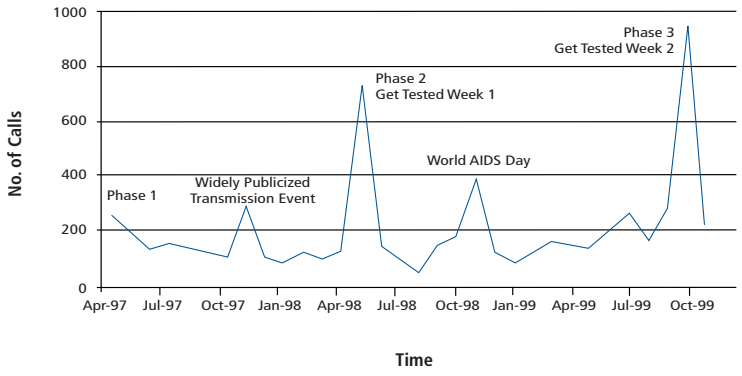

Figure **4.** Number of telephone calls to Project ACCESS hotline from 1997 to 1999. Courtesy of Donna C. Futterman, MD.

REACH, an observational study; Project TREAT, an initiative promoting adherence to medical treatment; and Project ACCESS, a social marketing initiative promoting counseling and testing. Project TREAT focuses on staging individuals according to their level of treatment readiness according to Prochaska's stages of change model and supports adherent behavior through a number of measures, including practice trials with vitamins. The project adopts the philosophy that adolescents are ideal targets for early intervention since they have been infected relatively recently in most cases. Treatment is based on adult guidelines, with the Tanner staging of puberty used to judge appropriate dosing. The project also adopts the philosophy that the best regimen is the regimen that will be adhered to, using the motto "keep it simple and safe" (KISS).

Project ACCESS was established in New York City and has since been initiated in 5 additional cities. The goal of the project is to identify HIV-infected youth and link them to health care by normalizing HIV counseling and testing among sexually active youth and encouraging routine counseling and testing by health care providers. Unlike many prevention programs, the program seeks to reinforce the role of HIV counseling and testing in prevention. The current ACCESS social marketing program is entitled "HIV. Live with it. Get tested." The program advertising for the New York initiative uses euphemisms for sexual activity used by the target age group, such as "gettin' busy." Other project components consist of youth leadership, including peer outreach workers and spokespeople; "Get tested! Week," which facilitates media focus and community organizing; and use of new testing technologies–eg, oral testing that will permit testing in nonmedical sites. In 1999, the New York project had 120 community partners and 70 testing sites. A meeting organized by ACCESS in 1999 brought approximately 500 youth together to talk about HIV at the Apollo Theater in Harlem. Overall, between 1997 and 1999, the New York program hotline has received 6600 calls, and at least 200 youth have been tested for HIV infection. As shown in Figure 4, numbers of calls increased dramatically in association with the wide publicity of the upstate New York case mentioned above, World AIDS Day, and the program's 2 "Get tested! Week" initiatives during this period.

Overall, it is believed that the approach to prevention in adolescents should follow a harm reduction model. Elements of a safer sex continuum should be emphasized, including abstinence, "outercourse" (masturbation or other sex without exchange of body fluids), and barrier methods. Other components of risk reduction in this age group should include emphasis on partner negotiation and decision making and the continuum from abstinence to safer sex.

Policy issues to be confronted in improving prevention, identification, and treatment efforts include those related to development of realistic prevention programs that include counseling and testing; outreach initiatives and linkage to health care; and development of youth-centered programs that address the issues of confidentiality and parent notification, appropriate treatment, and peer and psychologic support. Access to funding for prevention and treatment programs is, of course, a major policy issue.

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Upcoming Events of the International AIDS Society–USA

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

ICAAC Interactive Symposium

International AIDS Society–USA Symposium at the 40th Annual ICAAC:
Current Issues in the Management of HIV-Infected Patients: A Case-Based, Interactive Program

Tuesday, September 19, 2000
Metro Toronto Convention Centre, Toronto, Ontario, Canada
Chairs: Constance A. Benson, MD, and Paul A. Volberding, MD

IDSA Interactive Session

International AIDS Society–USA Interactive Session at the 38th Annual IDSA Meeting:
Management of HIV Infection

Saturday, September 9, 2000
Ernest N. Morial Convention Center, New Orleans, Louisiana
Chairs: William G. Powderly, MD, and Michael S. Saag, MD

Sixth Annual Fall CME Course Series

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

Thursday, September 28, 2000
New York Hilton and Towers, New York, New York
Chairs: Douglas T. Dieterich, MD, and Roy M. Gulick, MD, MPH
Early Registration Fee: $35

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 panel of HIV/AIDS experts. Topics will include updates on HIV pathogenesis, new drugs and regimens, strategies for managing antiretroviral failure, and the changing course of HIV disease.

Additional courses will be held in Chicago, San Francisco, and Los Angeles.

Cases on the Web - http://hivinsite.ucsf.edu/iasusa/cme

A collaboration of the International AIDS Society–USA and HIV InSite, *Cases on the Web* is an ongoing series of case-based, advanced online CME activities sponsored by the International AIDS Society–USA.

Cases Now Available:

Metabolic Complications of Antiretroviral Therapy
Frank J. Palella, MD
Guest Editor: Steven K. Grinspoon, MD

Resistance Testing in Antiretroviral Management
Michael S. Saag, MD
Guest Editor: Daniel R. Kuritzkes, MD

Clinical Management Issues in Antiretroviral-Experienced Patients
Paul A. Volberding, MD

For information about any of these programs, please contact the International AIDS Society–USA
Symposium Voice Mail: (415) 561-6725 • Fax: (415) 561-5740 • E-mail: info@iasusa.org

A publication of the International AIDS Society–USA

Upcoming Events

International AIDS Society–USA Symposium at the 40th Annual ICAAC:
Current Issues in the Management of HIV-Infected Patients: A Case-Based, Interactive Program

Tuesday, September 19, 2000
Toronto, Ontario, Canada

International AIDS Society–USA Interactive Session at the 38th Annual IDSA Meeting:
Management of HIV Infection

Saturday, September 9, 2000
New Orleans, LA

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

Thursday, September 28, 2000
New York, NY

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San Francisco, CA 94129-0916

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