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IMPROVING THE MANAGEMENT OF HIV DISEASE®

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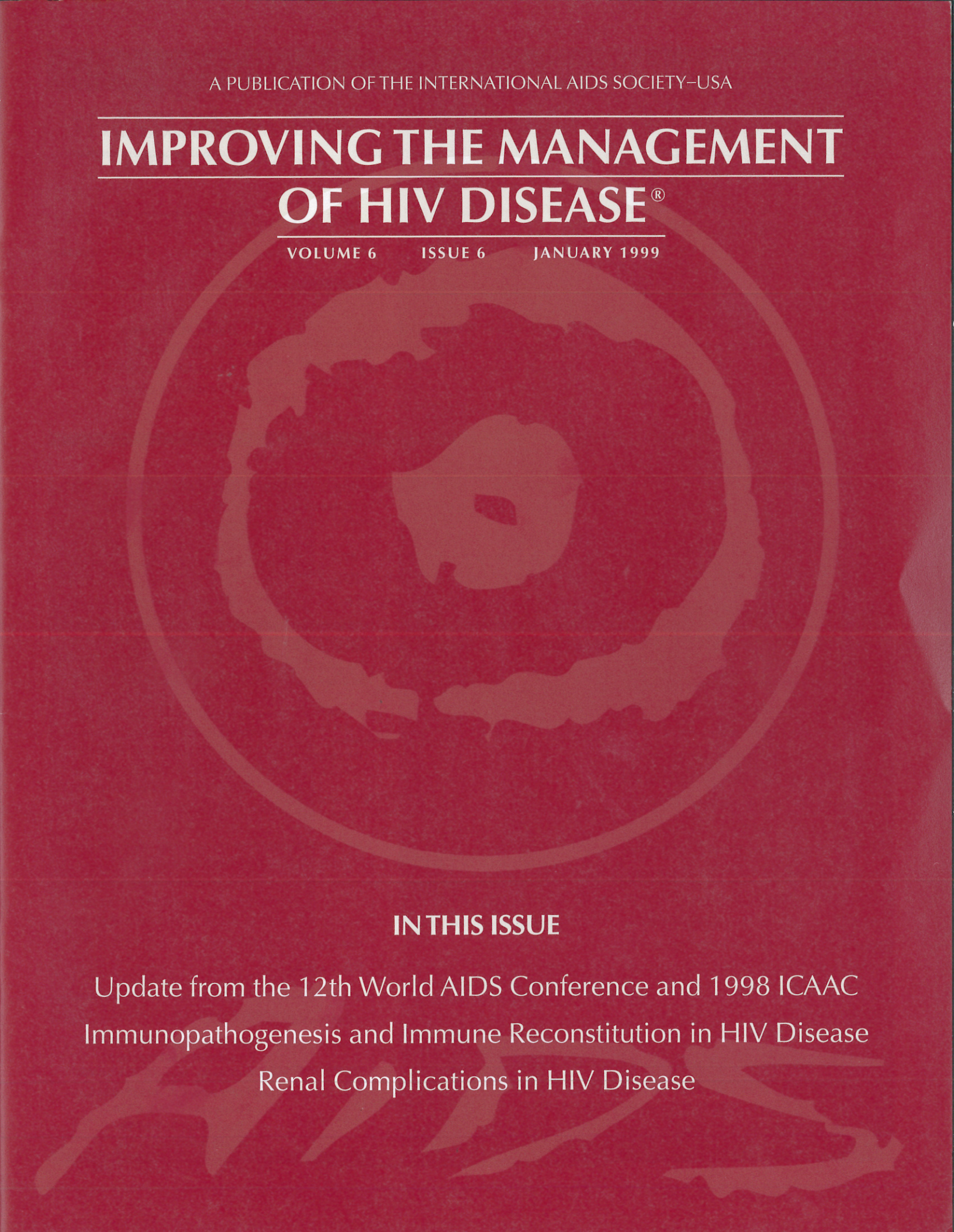

IN THIS ISSUE

ABOUT THIS ISSUE...

This issue of *Improving the Management of HIV Disease* highlights three talks given at International AIDS Society–USA-sponsored CME courses held in October of 1998. The courses were designed to provide information for physicians and other practitioners who are actively involved in HIV/AIDS clinical care or research.

Dr Bruce Walker reviewed the recent findings relating to the immunopathogenesis of HIV infection, with a focus on the association of HIV-1 specific T-cell response and cytolytic T-cell response among individuals who exhibit control of viremia in the absence of antiretroviral therapy. The second article summarizes key new data presented at two recent major research conferences, the World AIDS Conference in Geneva and the 38th annual ICCAC meeting in San Diego, with a focus on antiretroviral therapy and the role of PCP prophylaxis in the era of potent antiretroviral therapy, as reviewed by Dr Judith Currier. Finally, Dr Paul Klotman presented an update of the renal complications of HIV disease and its treatments — a topic of increasing importance in this field.

This issue also provides the first announcement of the International AIDS Society–USA Web site (see page 16). Please bookmark the address: http://www.iasusa.org and check back in March. Also, please see page 15 for the 1999 schedule of CME courses.

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CONTENTS

Immunopathogenesis and Immune Reconstitution in HIV Disease

At the New York course, Bruce D. Walker, MD, discussed recent findings on the association of HIV-1-specific T-helper-cell response and cytolytic T-cell response in HIV-infected individuals who exhibit control of viremia in the absence of antiretroviral therapy.

Some patients with HIV-1 infection exhibit no apparent disease progression and plasma viremia below limits of detection of available assays in the absence of antiretroviral therapy. Attenuated viruses and host genetic factors account for only a minority of cases of nonprogressing or slowly progressing disease. In many of the cases of long-term disease-free survival, strong cytolytic T-lymphocyte (CTL) responses to infection are maintained throughout the course of infection, suggesting that host immune response can successfully contain HIV-1 replication. It has recently been found that this response is associated with HIV-specific T-helper-cell activity. Continued elucidation of the mechanisms of successful host response to HIV-1 infection may result in effective immune-based therapies and contribute to the development of anti-HIV vaccine.

CTL Response to Infection

Attenuated HIV-1 and such host genetic factors as chemokine receptor polymorphisms that limit the ability of host cells to become infected appear to account for a minority of cases of nonprogressive HIV-1 infection. Studies of HIV-1-specific immune response have shown that neutralizing antibody may be present in low to undetectable levels in individuals spontaneously controlling HIV-1 infection, indicating that antibody response alone is not sufficient to control viral replication.

There are substantial data in a number of viral systems indicating that CTLs constitute a major component in controlling viral replication. Studies in vitro have shown that addition of single CTL clones specific for a single HIV-1 protein to HIV-1-infected CD4+ cell in culture can produce a 10,000-fold decrease in virion production compared with control culture and that no viral replication is observed with removal of CTLs from culture at 14 days. This antiviral effect is initiated by CTL T-cell-receptor-mediated recognition of processed viral protein presented in the context of an MHC class I molecule on the surface of the infected cell. Direct lysis of the infected cell occurs through CTL production of granzymes and perforin; the activated CTL also bathes the local microenvironment with antiviral factors (beta-chemokines and other soluble factors) that can inhibit virions already produced by the infected cell. Studies of viral dynamics indicate a span of approximately 2.5 days between infection of a cell and budding of progeny virions at the cell surface, during which time viral proteins are being degraded and presented at the cell surface. Recognition of the viral antigen by CTLs during this process may result in cell lysis prior to production of progeny virions and, thus, elimination of virus. The ability of CTLs to control infection depends on cell number and activation state. Attempts to restore the CTL immune response in individuals with chronic infection via infusion of HIV-1-specific CTLs have met with only limited success, probably because the infused cells do not achieve the proper activation state in vivo.

Studies of HIV-1-infected individuals have shown that the CTL response occurs early after the acute infection period. In rapid progressors, this response appears to dissipate rapidly shortly thereafter, whereas nonprogressors appear to maintain a strong response broadly directed against multiple viral proteins even in the absence of antiretroviral therapy (Figure 1). With use of a novel technique for quantitating CTLs in peripheral blood, it has very recently been demonstrated that the number of CTLs is correlated with viral load, providing evidence that this immune response is associated with control of viremia. This technique involves staining of HLA class-I peptide tetramers, consisting of streptaviden bearing four MHC class I molecules and viral peptide, that bind to the CTL surface. The labeled complexes can be directly visualized, with flow cytometry providing a rapid and accurate measure of CTL number. The tetramer staining is significantly correlated with viral load in infected individuals who never received antiretroviral therapy: those with low viral loads have higher tetramer staining, and those without high viral loads have lower tetramer staining.

> *It has recently been demonstrated that the number of HIV-1-specific CTLs is correlated with plasma viral load in patients not receiving antiretroviral therapy*

Role of T-Helper Cells in CTL Response

The demonstration that increased CTL activity and number are associated with control of HIV-1 viremia has led to attempts to identify the mechanisms controlling the activation state and the magnitude of response of CTLs in vivo. Studies in other viral systems have shown that virus-specific T-helper cells are a critical component in effective control of viral replication. These cells are CD4+ cells that recognize antigen on cell surfaces via the T-cell receptor and interaction with

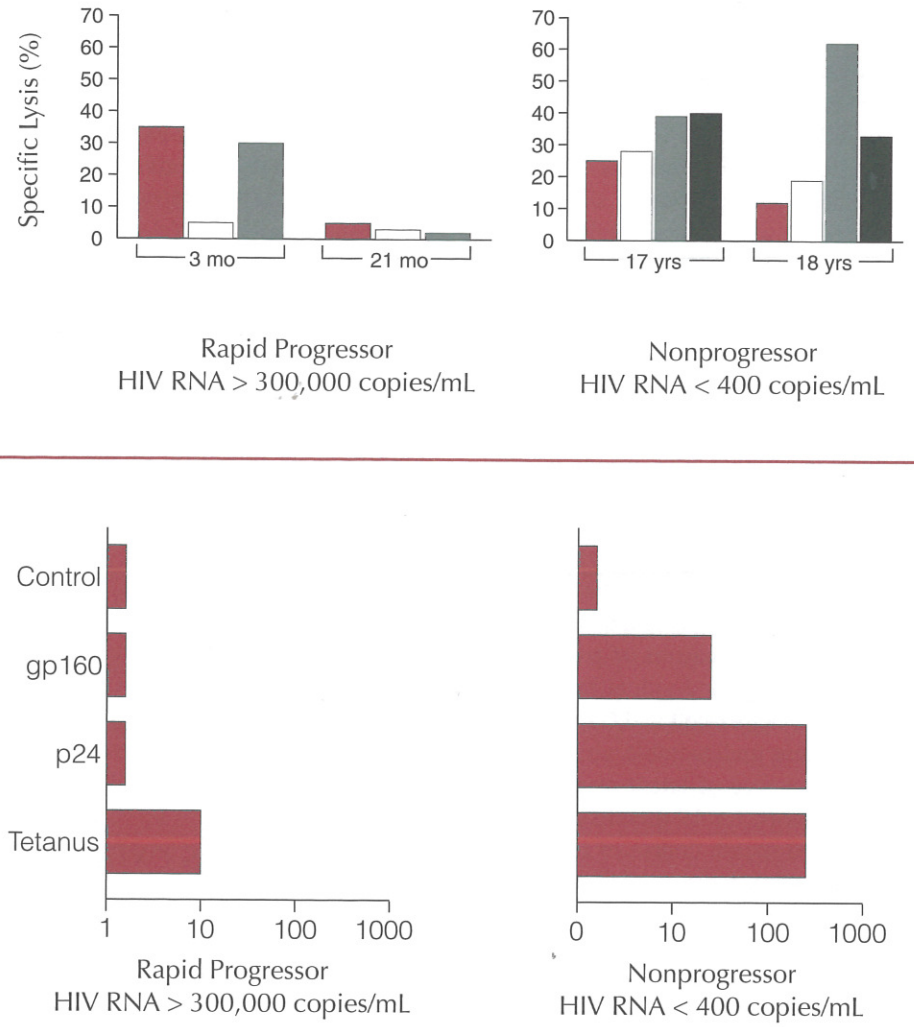

Figure 1. *HIV-1-specific CTL and T-helper-cell responses in a patient with rapid disease progression and in a patient with nonprogressing infection. The rapid progressor exhibited a rapid CD4+ cell decline, development of AIDS at 13 months after primary infection, and consistently high plasma viral load (>750,000 RNA copies/mL). The nonprogressor remains well at 19 years, with a CD4+ cell count of 1000/μL and viral load <400 RNA copies/mL.* ***Top****, percent lysis by CTLs specific for reverse transcriptase (RT), Gag, Env, and Nef proteins of HIV-1 in rapid progressor at 3 and 21 months and in nonprogressor at 17 and 18 years.*

Bottom*, stimulation index for specific T-helper-cell responses to HIV-1 gp160 and p24 and tetanus antigen, compared with control condition, in rapid progressor and nonprogressor.*

the CD4 molecule on the helper cell surface; this interaction stimulates lymphokine secretion and cell-cell interactions that orchestrate CTL function, B-cell function, antibody production, natural-killer-cell function, antigen presenting cell (APC) function, and cytokine production. In such animal models as murine lymphocytic choriomeningitis virus infection, viral replication is suppressed in association with a CTL response in intact animals; however, in CD4-depleted or CD4-knockout animals, the initial CTL response is followed by a decline in CTL activity and increased viremia. It is of interest that in vitro study of the HIV-1-specific T-helper cells has shown that p24 stimulation results in a 10- to 100-fold increase in production of antiviral beta chemokines by these cells, compared with low-level production in control experiments, indicating that these helper cells are also directly active in limiting spread of infection.

HIV-1-specific T-helper-cell responses appear to occur early in infection and to be lost shortly thereafter in the majority of infected individuals. This loss occurring early in infection represents a dramatic immune system deficit and occurs in the context of preserved specific T-helper-cell responses to such viruses as cytomegalovirus and Epstein-Barr virus. Recently, Rosenberg and colleagues investigated T-helper-cell response in a unique group of infected persons who were maintaining viral loads below the limits of detection without the need for antiviral therapy. Peripheral blood lymphocytes from such individuals were stimulated with HIV-1 antigens and incubated for 6 days; cell uptake of subsequently added tritiated thymidine was measured as an index of helper cell proliferation, with proliferation serving as an index of cell function. Figure 1 shows the

HIV-1 p24-specific T-helper cell function and plasma viral load have been found to be significantly correlated

T-helper-cell response in a nonprogressor who is spontaneously controlling viremia, compared with a rapid progressor; as can be seen, the nonprogressor exhibits a strong HIV-1-specific T-helper cell response (as measured by stimulation index) to both viral proteins, whereas the rapid progressor exhibits virtually no response to viral proteins and a reduced response to tetanus antigen. Assessment of relationship between viral load and HIV-1

p24-specific helper cell function in 10 subjects showed a highly significant correlation between the two measures (Figure 2). Subsequent investigation showed that CTL response (to gag protein) was significantly correlated with level of HIV-1-specific T-helper-cell activity.

Association of Early Treatment and T-Helper-Cell Response

The association between CTL activity and T-helper-cell activity and the absence of T-helper-cell response in progressive infection suggests that loss of or failure to mount and maintain an effective immune response may be explained by infection and depletion of the activated T-helper cells during acute infection. These cells are primary targets of HIV-1 infection, and their loss may result in insufficient activation of CTLs and failure to maintain function of generated CTLs. In an ongoing study, individuals presenting with acute HIV-1 infection are receiving immediate treatment with potent (triple-drug) antiretroviral therapy and are assessed for T-helper-cell activity with the hypothesis that protection of the T-helper-cell population during acute infection may lead to preserved function after the acute phase. The absence of p24-specific helper cell activity during the acute retroviral syndrome and a robust response was observed at 3 months in one of these patients, along with the correlation of viral burden and specific helper cell activity in this individual (Figure 3). During the acute retroviral syndrome, only 3 of 20 patients showed significant specific T-helper-cell activity with a stimulation index of >10. Responses increased in all individuals followed up for 2 months, with 11 of 15 having a stimulation index of 10 to 100. Responses in this range have been observed in 9 of 10 individuals at 6 months and in each of 4 followed for 1 year (stimulation index range at 1 year, 30 to 167). These findings suggest that early potent antiretroviral therapy may serve to permit an effective immune response that is otherwise observed only in individuals exhibiting spontaneous immune system control of infection.

Whether early effective treatment permits an immune response of sufficient quality or magnitude to result in continued control of infection in the absence of continued treatment is currently being investigated at Dr Walker's institution. The potential for early therapy to contribute to maintained immune system control of infection is suggested by findings in an acute pathogenic HIV-2 model. In one study, infected control animals were dead at 6 months, whereas five of six animals receiving 16 weeks of stavudine treatment remain alive with control of viremia and normal CD4+ counts at 3 years. In individuals with HIV-1 infection, anecdotal reports suggest that early therapy may influence outcome in at least some persons. Reported studies include those of rebounds of viremia after discontinuation of treatment in patients who started therapy early in infection, including one individual in whom the primary infection syndrome recurred but who had no evidence of specific CTL responses at the time of discontinuation of treatment. However, another individual has exhibited strong T-helper-cell and CTL activity and persistent undetectable viremia, despite the presence of latent reservoirs of infectious virus, for 19 months after cessation of a 6-month course of treatment.

Information from studies of the nature of immune response with early treatment may provide help in determining how immune reconstitution might be best attempted in patients with chronic progressive infection. There is some evidence to suggest that some recovery of T-helper-cell function may be observed over the course of years of treatment in individuals with chronic infection, with some recovery of naive cells in the periphery and lymph nodes having been observed. It is currently being investigated whether there is recovery of naive cells during prolonged effective therapy that might permit induction of HIV-1-specific helper cell responses through use of a therapeutic vaccine. Investigations of therapeutic vaccination have typically occurred in individuals with high levels of viremia; it is believed that proliferative response of T-helper cells in such patients would be countered by infection of these target cells in the setting of the high plasma viral load. It is also to be noted that although

Early potent antiretroviral therapy may result in immune response like that in individuals exhibiting spontaneous control of infection

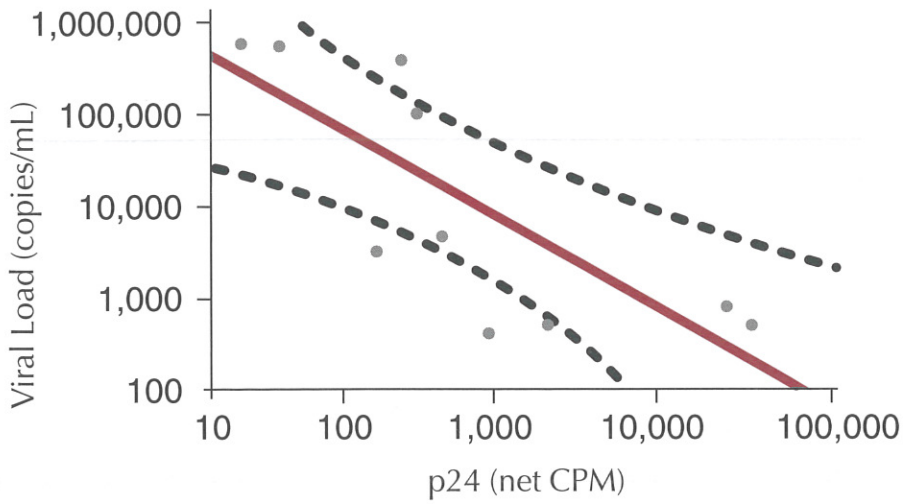

Figure 2. *Correlation of HIV-1 p24-specific T-helper-cell function and plasma viral load in individuals with chronic infection.(R = .80; P<.006). Adapted from:* Science *(Rosenberg et al).*

low-level ongoing viral production in individuals with controlled viremia might be expected to stimulate immune system response to viral antigen, suggesting the potential lack of utility of vaccine stimulation, it may be that the level of stimulation in such individuals is too low for maintenance of a specific immune response. There is some evidence, for example, that antibody response to viral components wanes over time in patients in whom viral replication is suppressed.

Studies of immune response with early treatment may provide help in efforts at immune reconstitution in chronic progressive infection

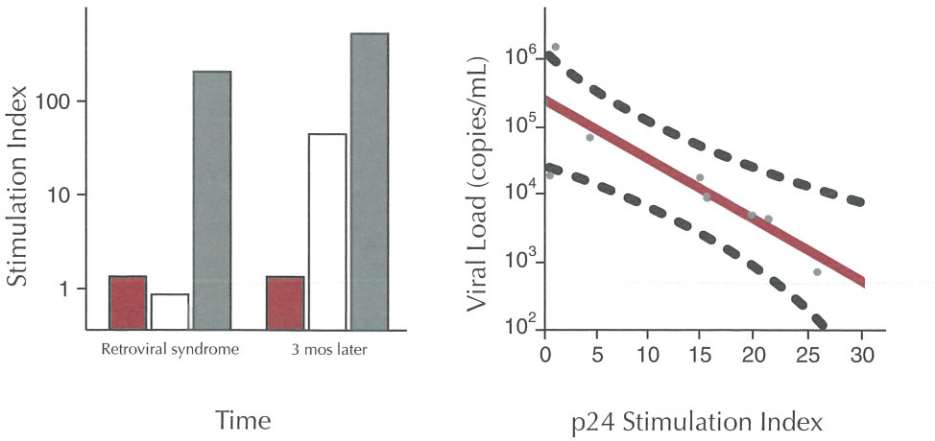

***Figure 3. Left**, HIV-1 p24-specific T-helper-cell response compared with response to PHA stimulation and control condition (stimulation index) during primary infection syndrome and at 3 months in individual receiving triple-drug antiretroviral therapy during acute infection. **Right**, correlation of p24-specific T-helper-cell function and plasma viral load in this individual. (R=-.85; P<.008). Adapted from:* Science *(Rosenberg et al).*

Summary

Long-term spontaneous control of HIV-1 viremia is associated with maintenance of strong HIV-1-specific T-helper-cell and CTL responses. Individuals with chronic infection lacking a strong CTL response have been found to exhibit low T-helper-cell activity. The initial T-helper-cell response is lost during acute infection of most patients, possibly because of infection and depletion of activated helper cells by HIV. Early potent antiretroviral therapy may produce (or protect,) immune responses similar to those observed in individuals with spontaneous control of viremia by protecting activated helper cells during acute infection. This protective effect may allow maintenance of the population of functional HIV-1-specific helper cells and thus maintenance of the HIV-1-specific CTL activity dependent on helper cell function.

It remains to be determined, however, whether patients treated in the acute stage of infection who develop and maintain strong T-helper-cell responses can control viral replication without antiretroviral therapy. Other important issues to be addressed include whether prolonged treatment with potent antiretroviral therapy permits restoration of T-helper cells in patients with chronic infection and/or whether the immune system in such patients can be appropriately boosted to achieve immunologic control of infection.

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Suggested Readings

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Update from the 12th World AIDS Conference and 1998 ICAAC

At the San Francisco course, Judith S. Currier, MD, summarized some recent findings in antiretroviral therapy studies reported at the 12th World AIDS Conference (AIDS Conference) and the 1998 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC).

Much recent investigation of antiretroviral therapy has focused on new drugs and novel combinations of available agents. The number of options in initial and subsequent therapy has increased, and some recent findings may help to provide guidance in selection of appropriate treatment. Select studies of regimens containing nucleoside reverse transcriptase inhibitors (nRTIs), nonnucleoside RTIs (NNRTIs), and hydroxyurea without protease inhibitors, protease inhibitor-based regimens, and protease inhibitor combination regimens are reviewed herein. Dr Currier expressed caution about the interpretation of data from trials of potent antiretroviral regimes. Specifically, many of the studies differ in trial design, stage of disease, treatment histories of the study subjects, and methods of analysis. In addition, the open-label or limited nature of many of the trials do not permit assessments of relative efficacies among different potent regimes. Also briefly reviewed are reports of early findings of effects of stopping prophylaxis for *Pneumocystis carinii* pneumonia (PCP).

Hydroxyurea, nRTI, and NNRTI Regimens

There is considerable interest in protease inhibitor-sparing initial antiretroviral regimens due to (1) concerns over protease inhibitor-associated complications, (2) the desire to preserve therapeutic options in subsequent treatment, (3) the availability of non-protease inhibitor-containing regimens that exhibit efficacy equivalent to protease inhibitor-based regimens, and (4) favorable dosing requirements of protease inhibitor-sparing regimens.

Hydroxyurea-Containing Regimens

The 6-month findings of a comparison of didanosine/zidovudine, didanosine/stavudine, didanosine/hydroxyurea, and didanosine/stavudine/hydroxyurea showed that the triple-drug regimen was associated with a significantly greater proportion of patients with plasma HIV-1 RNA level maintained at <400 copies/mL (75%) (Federici et al, AIDS Conference, abstract 12235). Lori and colleagues presented long-term follow-up in a group of patients taking hydroxyurea/didanosine showing continuing decreases in viral load in patients remaining on therapy, from 1847 RNA copies/mL at week 40 to 254 copies/mL at week 122.

nRTI-Containing Regimens

The 6-month findings in the ALBI study indicate that the combination of didanosine/stavudine was associated with viral suppression (50% of patients at <40 RNA copies/mL) superior to that of zidovudine/lamivudine or didanosine/stavudine for 3 months followed by zidovudine/lamivudine, indicating the utility of this nRTI combination as a backbone of potent antiretroviral therapy (Molina et al, AIDS Conference, abstract 12227). Preliminary 6-month findings of the GW Study CNAA 3003 in treatment-naive patients (median HIV RNA of 32,000 copies/mL, median CD4+ cell count of 438/μL) suggest that abacavir/zidovudine/ lamivudine is associated with a greater viral suppression than zidovudine/lamivudine (HIV RNA level <400 copies/mL in 60% to 70% vs. 30% to 40%) (Hammer et al, ICAAC, abstract S-3). Analysis at 16 weeks showed that viral suppression was achieved with the triple-drug regimen in patients with higher viral loads (reduction to <400 HIV RNA copies/mL in 76% with pretreatment viral loads <10,000 copies/mL vs. 67% with >100,000 copies/mL) (Fischl et al, AIDS Conference, abstract 12238). Continued experience indicates that the frequency of abacavir hypersensitivity reaction remains at about 3%. This systemic reaction typically occurs in the first weeks to months of treatment, and is frequently associated with fever (70% of definitive cases), rash (55%), and nausea (30%) (Hetherington et al, AIDS Conference, abstract 12353); the reaction warrants immediate drug discontinuation and fatal reactions to rechallenge have been observed if the drug is restarted. Therefore, rechallenge should not be attempted.

> *Data from the INCAS trial support the importance of nadir viral load in maintaining durable virologic response to treatment*

NNRTI-Containing Regimens

The recently reported 1-year findings of the INCAS trial indicate the marked superiority of plasma viral suppression with nevirapine/zidovudine/didanosine (approximately 50% of patients had viral load reductions to <20 HIV RNA

copies/mL) compared with zidovudine/didanosine or zidovudine/nevirapine (Montaner et al, *JAMA* 1998;279:930). Data from this trial, in which patients achieving this high level of viral suppression maintained it throughout follow-up, add to the evidence indicating the importance of the nadir viral load achieved in maintaining durable virologic response to treatment and, thus, the importance of initiating therapy with the most potent available regimens. Figure 1 shows time to loss of virologic response according to peak response in study patients.

A small study has shown that 16-weeks of nevirapine/stavudine/once-daily didanosine is associated with a 1.8-log decrease in HIV RNA level and a 139 cell/μL increase in CD4+ count (Raffi et al, AIDS Conference, abstract 12239). Another study in a small number of patients indicates a reduction in viral load to <500 RNA copies/mL in >90% of patients at 6 months and a large CD4+ cell count increase (>150/μL) with nevirapine/didanosine/lamivudine each given once daily (Haberi et al, AIDS Conference, abstract 22398). Finally, a study of response to protease inhibitor-containing regimens in a small cohort of patients developing high-level nevirapine resistance showed a median reduction in viral load of 1.54-log HIV RNA copies/mL, with a range of 0.03 to 3.13 log, and a median increase in CD4+ cell count of 96/μL, with a range of -108 to +776/μL (Curry et al, AIDS Conference, abstract 12231); the observation of a wide variation in response provides support for the contention that the best virologic response is achieved with initial therapy and that the ability to switch to maximally suppressive therapy cannot always be assumed.

Prior experience with the NNRTI delavirdine generally has been in combination with zidovudine or didanosine in treatment-experienced patients. The 1-year findings in a study comparing delavirdine/zidovudine/lamivudine with delavirdine/zidovudine and zidovudine/lamivudine in treatment-naive patients indicate marked superiority of the triple regimen in viral suppression (approximately 60% of patients with HIV RNA <40 copies/mL) (Para et al, AIDS Conference, abstract 12219).

The NNRTI efavirenz has recently become available. The 36-week outcomes of a trial comparing efavirenz/zidovudine/lamivudine, efavirenz/indinavir, and indinavir/zidovudine/lamivudine provide some measure of the comparative effectiveness of protease inhibitor-sparing and protease inhibitor-containing regimens (Staszewski et al, AIDS Conference, abstract 22336). Treatment-received analysis indicates that HIV RNA levels were reduced to <50 copies/mL in 88% of patients receiving the efavirenz-containing triple-drug regimen and in 82% of the indinavir-containing triple regimen group (and 67% of the efavirenz/indinavir group). An intent-to-treat analysis using the last-observation-carried-forward method showed that respective proportions of patients achieving this level of suppression in the triple-drug groups were 66% and 50%, a significant difference favoring the efavirenz-containing regimen (52% in the efavirenz/indinavir group); on intent-to-treat analysis in which patients discontinuing study treatment were counted as treatment failures, viral suppression at this level was observed in 64% and 44% of patients, respectively (43% in the efavirenz/indinavir group). Significantly more patients prematurely terminated treatment with the indinavir-containing triple drug regimen than with the efavirenz-containing triple-drug regimen (30% vs. 25%), with significantly more experiencing adverse events (19% vs. 6%). Another study examining the effects of adding efavirenz to ongoing treatment with zidovudine/lamivudine showed that the resulting antiretroviral effect was transient, with median time to virologic fail-

A number of studies have shown that there are several protease inhibitor-sparing regimens that exhibit potent antiretroviral activity and have relatively simple dosing requirements

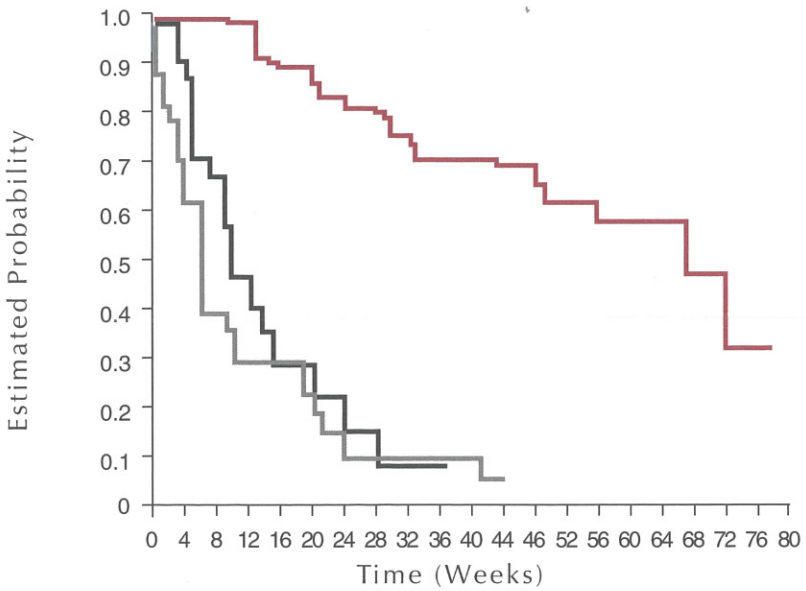

Figure 1. *Time from peak virologic response to first loss response, defined as increase in HIV RNA level to within 1 log of baseline, stratified by peak response in HIV RNA. Analysis is of didanosine/zidovudine and nevirapine/didanosine/zidovudine combined. Adapted from Montaner et al,* JAMA *1998;279:930.*

Table 1. Protease Inhibitor-Sparing Antiretroviral Regimens: Preliminary Studies

Regimen	Prior Treatment	Follow Up (Weeks)	Mean Decrease in HIV RNA	Percent of Patients Below Detection (HIV RNA assay)	Assay Detection Limits
			log copies/mL		HIV RNA copies/mL
delavirdine/zidovudine/ lamivudine[1]	No delavirdine, lamivudine, ≤6 months zidovudine	52	>2	75	400
stavudine/didanosine/ hydroxyurea[2]	None	24	2	75	400
efavirenz/zidovudine/ lamivudine[3]	No protease inhibitor, NNRTI, lamivudine	24	Not reported	86	400
abacavir/zidovudine lamivudine[4]	None	16	median 1.7	75	400
stavudine/didanosine nevirapine[5]	None	8	2	85	500

1. Para et al, AIDS Conference, abstract 12219. 2. Federici et al, AIDS Conference, abstract 12235. 3. Staszewski et al, AIDS Conference, abstract 22336. 4. Fischl et al, AIDS Conference, abstract 12230. 5. Raffi et al, AIDS Conference, abstract 12239. Please note that issues such as: trial design (open or randomized enrollment, size or length of the study); stage of disease; patient treatment histories; and methods of analysis and differences in activity of different potent antiretroviral regimens; do not permit assessments of comparative efficacies of different regimens from these data.

ure being 10 weeks (Meyers, AIDS Conference, abstract 22340). Resistance to efavirenz is mediated by single or double reverse transcriptase mutations. The addition of this drug to ongoing nRTI regimens in patients with detectable viral replication is not recommended.

A number of studies have thus shown that there are several protease inhibitor-sparing regimens that exhibit potent antiretroviral activity and have relatively simple dosing requirements. The virologic effects of some of these regimens are summarized in Table 1. Longer-term follow up with these regimens is eagerly awaited.

Protease Inhibitor-Based Regimens

Notwithstanding the rationale for protease inhibitor-sparing regimens in initial treatment, there are a number of reasons motivating initial treatment with protease inhibitor-containing therapy, including proven clinical efficacy and long-term viral suppression, high genetic barrier to resistance to these drugs, the evidence suggesting that the first treatment used should be the most potent, and the limited data on successful sequencing of drugs to support the strategy of reserving protease inhibitor treatment.

Initial protease inhibitor-based therapy continues to be motivated by a number of factors, including proven clinical efficacy and long-term viral suppression

Direct comparative data on protease inhibitor-containing regimens have begun to appear. One study in protease inhibitor-naive patients showed that HIV RNA levels <200 copies/mL were achieved in 82% of nRTI-naive and 77% of nRTI-experienced patients receiving indinavir, 64% and 77%, respectively, receiving ritonavir, and 95% and 81%, respectively, receiving ritonavir/saquinavir (Pederson et al, AIDS Conference, abstract 12221). The 6-month results of the CHEESE study indicate approximately 2.5-log HIV RNA reductions both with saquinavir soft gel capsule zidovudine/lamivudine and with indinavir/zidovudine/lamivudine (Borleffs et al, AIDS Conference, abstract 12267).

Data on potential alternative protease inhibitor dosing regimens have also begun to appear. A 32-week pilot study comparing standard indinavir tid dosing (800 mg tid) with 1000 mg and 1200 mg bid doses as part of triple-drug regimen

with zidovudine/lamivudine showed no difference in proportions of patients achieving viral suppression to <50 HIV RNA copies/mL.The subsequent larger-scale study was stopped and the bid dosing arm terminated when preliminary data at 24 weeks indicated reduction in HIV RNA levels to <500 copies/mL in 91% of the indinavir tid group vs. 64% of the bid group. Dr Currier noted that for patients who are already responding to indinavir bid, the convenience of the regimen may outweigh the risk of missing doses upon switching to the tid dosing. Pharmacokinetic analysis in a small subset of patients in a study comparing nelfinavir 750 mg tid and 1250 mg bid in combination with lamivudine and stavudine indicated that higher drug levels were achieved with bid dosing throughout the dosing interval. Study results at 48 weeks and 60 weeks indicate that approximately 80% of patients in both bid and tid dosing groups are maintained at HIV RNA levels <400 copies/mL.

Among studies evaluating NNRTI and protease inhibitor combinations, one in largely nRTI-experienced patients with high viral loads (mean, 5.1 log copies/mL; mean CD4+ cell count, 283/μL) showed that efavirenz/indinavir was associated with HIV RNA levels <50 copies/mL in 70% to 80% of patients at 84 weeks and striking CD4+ cell count increases (Havlir et al, ICAAC, abstract I104). Preliminary findings of another study, in which approximately half of the patients were nRTI-experienced (overall, mean HIV RNA of 37,000 copies/mL and CD4+ cell count of 370/μL), indicate that efavirenz/nelfinavir was associated with reductions in HIV RNA levels to <400 copies/mL in 60% to 80% of patients at 24 weeks (Kagan et al, ICAAC, abstract I102).

Some data on the investigational protease inhibitor amprenavir were also reported. Preliminary results in a study in treatment-naive patients (median HIV RNA, 4.6-log copies/mL; median CD4+ cell count, 420/μL) indicate that HIV RNA levels <400 copies/mL were achieved in 59% to 88% of patients taking amprenavir/zidovudine/lamivudine compared with 17% to 19% of those taking zidovudine/lamivudine at 16 weeks (Goodgame et al, ICAAC, abstract LB-5).

Table 2. Early Data on Stopping PCP Prophylaxis

Study	No. of Subjects	CD4+ count (cells/μL)	Follow Up	PCP Cases
Ravaux	40	>300	6 months	0
Reiss	68		34 patient-years	0
Vasquez	34	>200	9 months	0
Furrer	53	>200	5 months	0*
Schneider	50	>200	6 months	0

* Upper bound 95% confidence interval 13.3 cases/100 patient-years

Protease Inhibitor Combinations

The use of dual protease inhibitor therapy without inclusion of nRTIs remains controversial, although there are data indicating potent and prolonged virologic response in patients receiving such treatment. Treatment with ritonavir/saquinavir (bid or tid dosing) was associated with reduction of HIV RNA to <200 copies/ml in 90% of patients at 72 weeks, although many patients had taken nRTIs (usually stavudine plus lamivudine) added after 12 weeks (Mellors et al, AIDS Conference, abstract 12295). A study comparing ritonavir/saquinavir/stavudine and ritonavir/saquinavir with an nRTI added at or after week 12 for viral load >400 HIV RNA copies/mL showed that approximately 80% of patients in both arms had viral load <400 copies/mL at week 48, with some patients in the dual protease inhibitor arm having an nRTI added and this level of viral suppression being achieved more rapidly in a higher proportion of patients initially receiving the triple regimen (Gisolf et al, AIDS Conference, abstract 12274); since there appears to be an advantage to achieving maximal viral suppression as rapidly as possible, such findings support the initial inclusion of an nRTI in the regimen. The 48-week outcomes in another study indicate reductions in plasma HIV RNA to <50 copies/mL in 51% of patients taking saquinavir/nelfinavir/2 nRTIs, 42% receiving nelfinavir/2 nRTIs, 42% receiving saquinavir/2 nRTIs, and 35% receiving saquinavir/nelfinavir (Moyle et al, AIDS Conference, abstract 12222).

Attempts to reduce the total pill burden associated with protease inhibitor therapy and to arrive at optimal doses of protease inhibitors in combination continue. Pharmacokinetic analyses of combined indinavir and nelfinavir indicate that indinavir blood levels at a 1000 mg bid dose were not substantially different from those at 800 mg tid when administered in combination with nelfinavir 1000 mg bid. Studies are under way to determine whether higher doses of these drugs in combination are effective (1200 mg of indinavir, 1250 mg of nelfinavir). Another pharmacokinetic study is comparing indinavir 800 mg bid plus ritonavir 100 mg, 200 mg, or 400 mg bid and indinavir 400 mg plus ritonavir 400 mg bid in the setting of low-fat or high-fat meals. Early findings indicate that this combination is promising with coadministration of the drugs increasing indinavir blood levels substantially. Since sequential use of these two drugs would appear to be contraindicated due to their overlapping resistance patterns, combining them to im-

prove the pharmacokinetics of indinavir warrants further study.

Stopping PCP Prophylaxis

The use of highly potent antiretroviral therapy has resulted in reduction in the incidence of opportunistic infections, posing the issue of whether PCP prophylaxis can be stopped in patients taking effective antiretroviral therapy. A number of observational studies reported at the 12th World AIDS Conference have found no occurrences of PCP in short-term follow-up of relatively small groups of patients who decided to stop prophylaxis (Table 2). However, given the short follow-up time, the confidence interval for calculating the number of cases that could occur based on these observational data is very broad; in one study, the upper bound of the 95% confidence interval was a rate of 13.3 cases/100 patient-years. This issue currently is being evaluated in the ACTG 888 study. It is hoped that forthcoming data will allow determination of risk levels that permit discontinuation of prophylaxis and assessment of the potential impact of discontinuation of PCP prophylaxis on the incidence of other bacterial infections.

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Resources

Abstracts from the 12th World AIDS Conference; June 28–July 3, 1998; Geneva.

Abstracts from the 38th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 24-27; San Diego.

RENAL COMPLICATIONS IN HIV DISEASE

At the New York course, Paul E. Klotman, MD, presented a case of renal disorder in an individual with HIV disease. Details of the case presentation are summarized, followed by discussion of diagnosis and management.

CASE DESCRIPTION

Presentation

37-year-old black man, former injection drug user diagnosed as HIV-seropositive in 1986 and lost to follow-up, presents to AIDS clinic in 1996

Complaints

Recent cold, took some antibiotics
Malaise
Fatigue
Anorexia
Pruritus

Physical findings

Chronically ill-appearing thin man
Weight, 112 lbs; blood pressure, 120/70 mmHg; pulse, 84 bpm
No edema
Skin: several raised indurated lesions on chest, shoulders, and lower extremities with many excoriations; not typical Kaposi's sarcoma

Laboratory findings

Urinalysis: 2+ proteinuria, no sediment
CD4+ cell count, 30/μL
Creatinine, 3.5 mg%
Calcium, 8.2 mg%; phosphorus, 3.8 mg%
Albumin, 3.0 mg%
Hepatitis B and C negative
Plasma HIV RNA, 1.4×10^4 copies/mL

Diagnosis

In addition to a 24-hour urine test for creatinine clearance and protein excretion, initial workup of this patient included a renal ultrasound to evaluate the possibility of postrenal causes of decreased renal function (eg, urinary obstruction due to urethral stricture from recurrent sexually transmitted diseases). The patient exhibited some physical signs of dehydration, a common finding in patients who are infected with HIV-1. Renal biopsy was considered but postponed until obstruction could be ruled out and kidney size and number could be determined. Ultrasound results showed no evidence of hydronephrosis and 2 kidneys of 11 cm that appeared echogenic, a finding common in patients with HIV-associated nephropathy (HIVAN). Results from the timed urine collection revealed a creatinine clearance of 25 mL/min and 2.5 grams of protein excretion in 24 hours. Biopsy of skin lesions showed leukocytoclastic angiitis with some eosinophils, consistent with a drug reaction.

Based on these initial findings, the most likely diagnosis is HIVAN, so why is a renal biopsy required? This patient has many of the findings typically seen in HIVAN patients with renal disease who are biopsied. He is African American (90% of cases occur in blacks or Hispanics). He has a history of injection drug use (50% of HIVAN diagnoses), a physical exam consistent with volume depletion, significant proteinuria (>1 g), CD4+ cell count <200/μL, and normal to enlarged kidneys that are echogenic by ultrasound. In this case, additional diagnoses were possible although less likely, including heroin nephropathy, interstitial nephritis, lupus nephritis, and membranoprolifitive GN secondary to hepatitis. The rationale for biopsy, however, is that even in patients in which the diagnosis appears likely, only 60% will have HIVAN; 40% have some other renal histopathological diagnosis.

Renal biopsy was then obtained, which revealed FSGS (collapsing variant) with global sclerosis and microcystic dilatation, classic features of HIVAN, as well as mild interstitial infiltration and tubuloreticular arrays (Figure 1). When HIVAN is not found, the other diagnoses include focal and segmental glomerulosclerosis (FSGS) (10-15%), membranoproliferative glomerulonephritis (10%), and tubulointerstitial disease (7%), as well as a variety of other diagnoses.

Management

It may appear to be obvious, but the most reasonable first step in the treatment of HIVAN is the initiation of potent antiretroviral therapy. Patients with HIVAN usually have advanced HIV disease, AIDS, and detectable plasma viral loads. Highly active antiretroviral therapy (HAART) is effective in delaying AIDS progression in patients without renal disease and should be instituted in patients with renal disease as well. The vast majority of published cases of HIVAN have occurred in patients with CD4+ cell counts below 200/μL; in 10 cases at Dr Klotman's institution, CD4+ cell counts have ranged from 0 to 200/μL (mean, 60/μL) and the majority of patients have had high plasma viral loads (mean, 7.4×10^5 HIV RNA copies/mL) despite treatment. Resistance to ongoing treatment

may be common in these patients; very recent findings indicate that the kidney harbors HIV-1, a factor that may contribute to resistance. While there are only anecdotal reports of renal benefits with HAART therapy in HIVAN patients, the possibility of viral replication in the kidney suggests that there is a potentially viable study. A randomized, controlled trial currently is under way to compare effects of different potent antiretroviral regimens on survival and renal function in HIVAN, which may address this point.

From the first description in 1984 to the most recent studies within the past 2 years, HIVAN remains a disease characterized by rapid progression. The time from diagnosis to dialysis or death can be measured in weeks to months. Patients who move to dialysis have a high mortality, usually 50% per year. Several treatment strategies have been employed; the two best studied include the steroids and angiotensin-converting enzyme (ACE) inhibitors. One study of steroid treatment involved 19 patients with biopsy-proven HIVAN, serum creatinine >2 mg%, and 24-hour urinary protein >2 g. These patients received prednisone 60 mg/d for 2 to 11 weeks. Results were encouraging after 2 to 14 weeks with a 20% decrease in serum creatinine in 17 of 19 patients and a decrease in urinary protein in 12 of 13 patients. Unfortunately, only 2 patients survived for greater than 1 year without progressing to ESRD. The use of ACE inhibitors for the treatment of HIVAN has met with greater success. One study compared progression to ESRD in 9 patients receiving captopril (6.25 mg tid increasing to 25 mg tid) and 9 control patients. The mean serum creatinine of both groups was 3.4 mg%, indicative of advanced renal disease. Urinary protein/creatinine ratio exceeded 5, suggesting significant glomerular proteinuria. Time to ESRD progression was 156 ± 71 days in treated patients and 37 ± 5 days in controls. The data demonstrate only modest benefit but suggest that earlier therapy may be appropriate. Another study compared changes in serum creatinine in 12 HIVAN patients receiving fosinopril 10 mg qd for 6 months with those in 8 patients refusing such treatment. This patient population had only mild renal insufficiency, with serum creatinine of 1.5 mg%. At week 24, serum creatinine had increased from 1.5 ± 0.5 to 7.0 ± 3.0 mg% in untreated patients and from 1.5 ± 0.3 to 1.7 ± 0.7 mg% in treated patients. Although impressive, interpretation of these findings is somewhat confounded by the absence of a randomized study design. The bad outcome in the control group may also have reflected differences in antiviral adherence, since these were patients who refused therapy. What is clear from these studies is there remains a need for randomized studies of steroid and ACE treatment in patients with HIVAN.

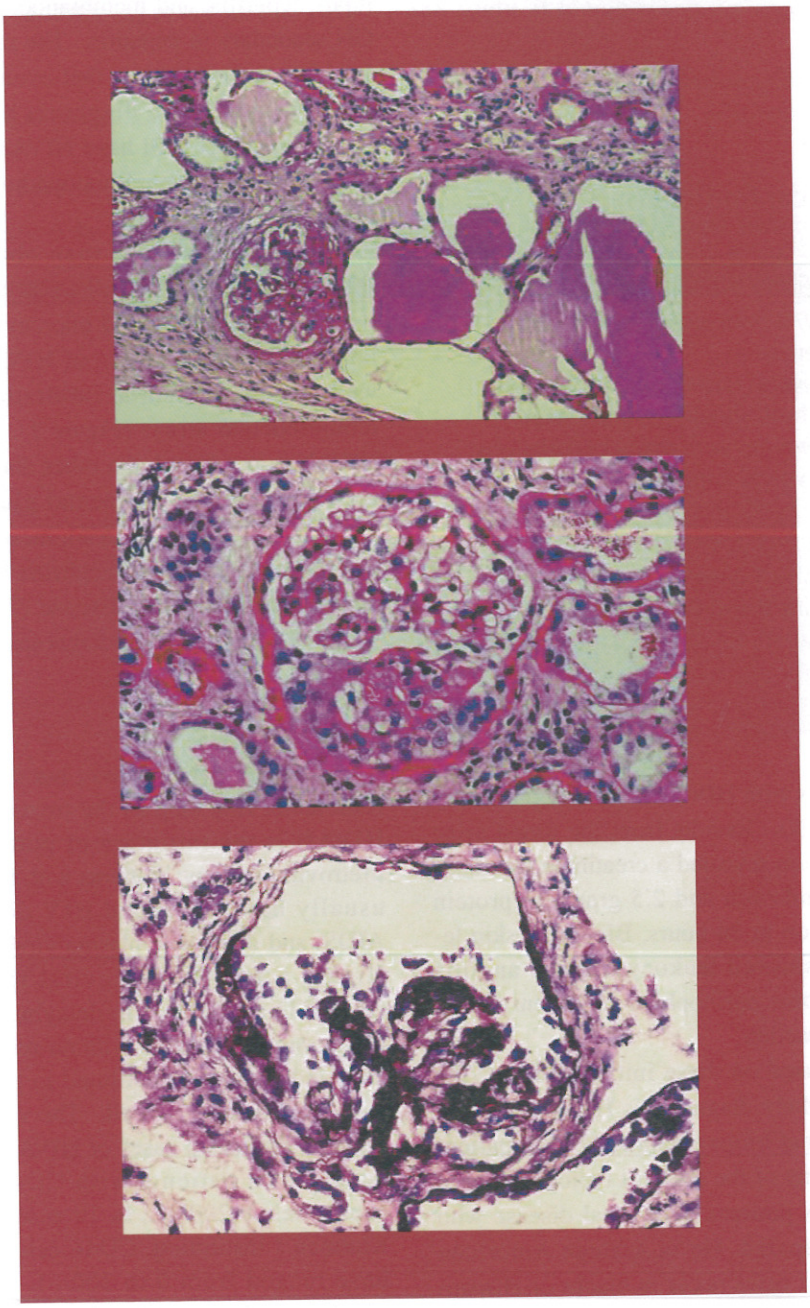

Figure 1. *Biopsy findings in case 1, showing microcystic tubulointerstitial disease* ***top****, focal and segmental glomerulosclerosis* ***middle****, and glomerulonephrosis, collapsing variant* ***bottom****.*

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Upcoming International AIDS Society–USA CME Courses

Winter/Spring 1999: Seventh Annual CME Program

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

This series reviews the most recent developments in the field of HIV disease pathogenesis and antiretroviral management. Expert faculty will speak on timely and clinically relevant issues in the management of HIV disease. Some topics include: new insights in HIV pathogenesis, strategies for antiretroviral management, new antiretroviral drugs and regimens, long-term complications of antiretroviral therapy, and HIV resistance testing.

1999 Winter/Spring Symposia Schedule		Early Registration Fees
Friday, February 12, 1999 JW Marriott Hotel Lenox Chairs: Michael S. Saag, MD, and Melanie A. Thompson, MD	**Atlanta, GA**	**$25.00**
Saturday, February 20, 1999 The Omni Los Angeles Hotel and Centre Chairs: Ronald T. Mitsuyasu, MD, and Paul A. Volberding, MD	**Los Angeles, CA**	**$25.00**
Saturday, March 6, 1999 Boston Marriott Copley Place Chairs: Scott M. Hammer, MD, and Robert T. Schooley, MD	**Boston, MA**	**$25.00**
Wednesday, March 24, 1999 New York Hilton and Towers Chairs: Gerald H. Friedland, MD, and Paul A. Volberding, MD	**New York, NY**	**$40.00**
Monday, April 12, 1999 The Ritz-Carlton San Francisco Chairs: Paul A. Volberding, MD, and Stephen E. Follansbee, MD	**San Francisco, CA**	**$25.00**
Wednesday, April 21, 1999 Sheraton Chicago Hotel and Towers Chairs: John P. Phair, MD, and Constance A. Benson, MD	**Chicago, IL**	**$25.00**
Saturday, May 8, 1999 Cleveland Marriott Downtown Chairs: Michael M. Lederman, MD, and Michael S. Saag, MD	**Cleveland, OH**	**$25.00**

National CME Course

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

This first annual course will be a state-of-the-art update on basic science, antiretroviral therapy, and complications of HIV disease. Four half-days of lectures and workshops will provide opportunities for in-depth discussions on complicated issues in HIV disease management. The course will take place in a relaxed and informal setting that will allow extensive time to meet the experts and review current topics in the field. This course is advanced level and is designed for physicians who are actively involved in HIV/AIDS care. Registration will be limited to 150 participants.

March 27-31, 1999 Snowmass Village, CO

For more information on any of these courses, please call the International AIDS Society–USA symposium voice mail at (415) 561-6725; fax at (415) 561-6740; or e-mail at cme@iasusa.org.

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We are grateful for their ongoing support and for their commitment to independent physician education.

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