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IMPROVING THE MANAGEMENT OF HIV DISEASE®

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ISSUE 2

MAY 1999

IN THIS ISSUE

Resistance Testing
Viral and Cellular Dynamics in HIV Disease
Treatment and Management of Antiretroviral Failures
Renal Complications

ABOUT THIS ISSUE...

Issue 2 of *Improving the Management of HIV Disease* marks the first regular issue of this volume. Summaries of 3 recent presentations given at the International AIDS Society—USA 1999 CME course series, *HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management*, are provided. The series of courses, now in its seventh year, offers timely and clinically relevant information for practitioners who are actively involved in HIV and AIDS clinical care or research across the country.

At the Atlanta course in February, Dr Daniel R. Kuritzkes discussed the emerging role of viral resistance testing. He outlined the relative advantages and disadvantages of genotypic and phenotypic assays, and explored the implications of the results of resistance testing for antiretroviral management. Also in Atlanta, Dr R. Pat Bucy provided an update on some provocative concepts in the area of viral and cellular dynamics of HIV-1 disease. At the New York course in March, Dr Scott M. Hammer reviewed current clinical strategies for maintaining optimal response to potent antiretroviral therapy, and for managing sub-optimal response and failure.

This issue also contains the second of two cases of renal complications presented by Dr Paul E. Klotman at the International AIDS Society—USA October 1998 course in New York. (See Volume 6, Issue 6 for case 1, covering HIV-associated nephropathy.)

Upcoming issues of *IMHD* will continue to provide summaries of

presentations given at recent International AIDS Society—USA courses. In addition, Issue 3 will offer special coverage of 4 basic science topics presented at the organization's first annual national CME course held in March, *The Science and Treatment of HIV*. Topics will include viral dynamics and HIV-1 reservoirs; the status of the thymus in adult HIV infection; the effects of therapy on immunologic parameters in acute and chronic infection; and novel targets for antiretroviral therapy.

For additional information on upcoming International AIDS Society—USA activities, please see page 19.

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RESISTANCE TESTING IN ANTIRETROVIRAL MANAGEMENT

At the Atlanta course, Daniel R. Kuritzkes, MD, discussed characteristics of genotypic and phenotypic resistance testing and the implications of testing for management of antiretroviral therapy.

The rapid turnover of HIV-1 and the high frequency of error of the HIV-1 reverse transcriptase result in great genetic diversity within the viral quasi-species. In the absence of selective drug pressure, virus with single mutations associated with antiretroviral drug resistance is constantly produced. Double mutations in an individual genome are of lower probability but are likely to occur with significant frequency, and triple mutations even less likely. Single mutations associated with resistance to antiretroviral drugs thus are likely to be present very early in infection and have been found in

Partial inhibition of virus with anti-retroviral therapy favors the emergence and dominance of resistant variants

patients who are antiretroviral-naïve. For some antiretroviral drugs (eg, lamivudine, nevirapine, efavirenz), single point mutations can confer high-level antiretroviral resistance, with drug pressure resulting in rapid selection of resistant mutants and loss of susceptibility within weeks of initiating incompletely suppressive treatment with regimens containing these drugs. For other drugs (eg, zidovudine and such protease inhibitors as indinavir and ritonavir), high-level resistance requires 3 or more

mutations within a single genome. Although single mutations may be present before treatment, accumulation of the multiple mutations conferring high-level resistance is step-wise and requires selective drug pressure.

Clinical experience has provided support for the idea that profound viral suppression with potent antiretroviral combinations delays or prevents emergence of resistance and that partial inhibition favors the emergence and dominance of resistant variants. A number of principles regarding development of resistance under combination therapy have begun to emerge. One is that trough plasma drug concentrations may be important in drug resistance; in the case of ritonavir, the higher the trough concentration of the drug, the more slowly resistance mutations emerge. In addition, the lower the nadir of plasma HIV-1 level, the longer it takes for drug failure to occur. An additional principle is that mutations selected by combination therapy may differ from those expected based on monotherapy experience with each component of the combination.

CHARACTERISTICS OF GENOTYPIC AND PHENOTYPIC ASSAYS

Genotypic analysis and phenotypic analysis, the fundamental approaches to assessing viral resistance, are associated with relative advantages and disadvantages. Current genotypic assays generally require samples with more than 1000 HIV-1 RNA copies, and only HIV-1 variants that constitute 20% or more of the viral population in the sample can be reliably detected. With current assays, all of which require initial amplification through polymerase chain reaction, false-positive results for specific mutations can occur due to carry-over of amplified product from other samples or random polymerase errors in nucleic acid synthesis. Relative advantages of genotypic analysis include its wider availability, briefer time to results (days to 2 to 3 weeks), and fewer technical demands, with much of the testing being automated and not requiring the cell

Like genotypic assays, phenotypic assays are insensitive for detecting resistant variants that constitute a minority of the viral population

culture needed for phenotypic assays. Genotypic analysis may also be more sensitive than phenotypic analysis in that the detection of a resistance mutation in some cases may precede identification of phenotypic resistance; in the case of drugs requiring multiple mutations for high-level resistance, detection of "sentinel" mutations is therefore possible.

Relative disadvantages of genotypic analysis include the fact that the assays provide an indirect measure of susceptibility. Prior investigation is needed to determine which mutations are responsible for phenotypic resistance, and such investigation is required for each new drug being tested, as well as for drug combinations. It also has been found that results on genotypic assessment sometimes do not correlate with phenotypic assay findings, likely due to as yet poorly understood aspects of resistance genotypes. In addition, expert interpretation of genotypic analysis may be required due to the large and growing database on resistance mutations.

With current phenotypic assays, a 4-fold change in 50% or 90% inhibitory concentration (IC₅₀ or IC₉₀) is the minimum change that is reliably detectable. Relative advantages of these assays include the fact that they provide a direct measure of drug susceptibility and that results are

expressed in the more familiar terms of IC_{50} and IC_{90} values. Limitations include restricted availability, with only 2 laboratories worldwide currently performing commercial phenotyping, and prolonged time to results (2 to 6 weeks) due to the labor-intensive work involved. Like the genotypic assays, phenotypic assays are insensitive for detecting resistant variants that constitute a minority of the viral population. Finally, clinically significant cut-off values for drug inhibitory concentrations have not been defined, and the clinical relevance of detection of IC_{50} and IC_{90} values for each drug used in combined regimens currently is unknown.

RETROSPECTIVE ANALYSES OF PREDICTIVE ABILITY OF DRUG RESISTANCE ASSAYS

A number of retrospective analyses have shown the ability of genotypic and phenotypic analyses to predict response to treatment. Lanier and colleagues demonstrated that the virological response to the nucleoside reverse transcriptase inhibitor (nRTI) abacavir was reduced in patients whose baseline virus carried zidovudine and lamivudine resistance mutations, mutations that had not been predicted to confer abacavir resistance in initial *in vitro* studies. Phenotypic analysis of virus isolates from these patients showed that decreased abacavir susceptibility correlated with a smaller decrease from baseline in plasma HIV-1 RNA level; it also showed that although the majority of patients responding to abacavir had abacavir-susceptible virus, many patients with susceptible virus did not have a good virologic response. Such a scenario, in which resistance is predictive of lack of response but susceptibility does not assure response, is common in the setting of antimicrobial treatment for bacterial infections (eg, mycobacterial infections).

Deeks and colleagues analyzed the significance of phenotypic drug resistance as measured by a recombinant virus assay (ViroLogic, Inc.) in patients in whom combination therapy that included indinavir was failing. Patients with plasma HIV-1 RNA levels greater than 2500 copies/mL who had received indinavir-containing therapy for more than 6 months were given a salvage regimen of saquinavir, nelfinavir, abacavir, and a

nonnucleoside reverse transcriptase inhibitor (NNRTI). At the time of the switch in treatment the median CD4+ count was 290 cells/ μ L and the median HIV-1 RNA level was 4.4 \log_{10} copies/mL. Results of the phenotype testing showed that patients with isolates sensitive to 1 or none of the drugs in the regimen had a 0.14-log decrease in plasma HIV-1 RNA level, whereas those with isolates sensitive to 2 or 3 drugs had a 2.25-log decrease ($P=0.007$).

Patck and colleagues conducted an analysis in a group of patients in the nelfinavir expanded access program who had failed other protease inhibitor treatment ($n=65$; mean CD4+ count of 110 cells/ μ L, mean plasma HIV-1 RNA of 4.58 log). Nelfinavir treatment resulted in a decrease in HIV-1 RNA of at least 0.5 log for 24 weeks in 14 of 32 patients for whom the analysis was performed. Genotypic analysis for the protease inhibitor resistance mutations G48V, V82A/T/F, I84V, and L90M in 28 patients showed that 16 of 19 with 1 or no mutations had a response to nelfinavir whereas only 3 of 9 with 2 or more mutations had a response ($P=0.013$). In a group of 84 protease inhibitor-experienced patients studied by Harrigan and colleagues, treatment with ritonavir and saquinavir led to a response

A number of retrospective analyses have shown the ability of genotypic and phenotypic analyses to predict response to treatment

in half. Genotypic and phenotypic analyses, each performed in approximately three quarters of patients, showed that 80% of patients with resistant isolates were nonresponders. Genotypic evidence of resistance conferred a more than 5-fold risk of treatment failure (odds ratio [OR]

5.6; $P<0.05$), and phenotypic resistance conferred a more than 3-fold risk of failure (OR, 3.4; $P<0.05$) compared with wild type. Breakthrough viruses had multiple mutations, including mutations at codons

In the GART study, HIV-1 RNA level decreased in proportion to the number of active drugs in the salvage regimen

10, 36, 48, 54, 71, 82, 84, and 90. Finally, Zolopa and colleagues reported on response to ritonavir/saquinavir in 51 patients in whom at least one prior protease inhibitor had failed; complete response (reduction of HIV-1 RNA to levels below detection [<500 copies/mL]) occurred in 37%, partial response (>0.5 -log reduction) in 27%, and no response in 35%. Predictors of response included disease stage, CD4+ cell count, and HIV-1 RNA at baseline ($P<0.03$), as well as number of prior protease inhibitors and RTIs used ($P<0.05$). Regression analysis showed that after accounting for prior therapy, the number of protease inhibitor resistance mutations was strongly associated with the likelihood of treatment response ($P<0.0001$), with the presence of 3 or more mutations at codons 30, 46, 48, 54, 82, 84, and 90 being highly predictive of a poor response.

PROSPECTIVE STUDY OF TREATMENT MODIFICATION

In addition to these retrospective analyses, there are now data from studies assessing the effects of changes in therapy based on genotypic analysis. In the Viradapt study, decreases in plasma HIV-1 RNA level over 6 months of treatment were greater in patients in whom treatment was guided by genotyping than in patients in whom regimens were selected without this knowledge. In the GART trial

(CPCRA 046), 153 patients with virologic failure (defined as a 3-fold increase in plasma HIV-1 RNA from baseline) after more than 12 weeks of treatment with 2 nRTIs and a protease inhibitor were randomized to genotyping combined with expert advice on choice of regimen or standard-of-care management without genotyping and advice; 73% of patients had major reverse transcriptase inhibitor and protease inhibitor resistance mutations, with 20% having reverse transcriptase inhibitor mutations with no protease inhibitor mutations and 4.6% having no resistance mutations. As reported by Baxter and colleagues, follow up at 12 weeks showed that decreases in HIV-1 RNA were 1.17 log in the genotyping group versus 0.62 log in the control group ($P=0.0001$). Plasma HIV-1 RNA levels were reduced to levels below the limits of detection (<500 copies/mL) in 29% of GART patients and 17% of controls ($P=0.15$). These early findings show that the magnitude of decrease in HIV-1 RNA level increased in association with number of active drugs in the regimen. Plasma HIV-1 RNA levels decreased by 0.25 log₁₀ copies/mL for each additional drug in the new regimen to which virus was susceptible. A total of 86% of patients in the genotyping arm received at least 3 active drugs, compared with 30% in the control arm. It was also found that although treatment changes were recommended in 86% of patients in the genotyping group, treating physicians implemented this advice in only 54% of cases.

DRUG FAILURE WITHOUT RESISTANCE

Despite the findings indicating the ability of genotypic and phenotypic analyses to predict response to treatment, it remains the case, as noted above, that not all drug failure is attributable to resistance. Recent

analyses by Holder and colleagues of isolates from time of onset of indinavir failure in patients receiving combined treatment with either lamivudine or efavirenz, have shown that indinavir resistance mutations are detected in a minority of cases. In 1 analysis of 23 patients in whom indinavir failed, only 5 exhibited indinavir resistance mutations, with 17 exhibiting lamivudine resistance mutations. In a similar analysis of 14 patients, indinavir resistance mutations were present in 3 cases, with 11 cases exhibiting efavirenz resistance mutations.

RESISTANCE IN PRIMARY INFECTION

Data from surveys of resistance in primary infection have recently been reported. Surveys of seroconverters in San Diego, Los Angeles, Dallas, Boston, and Denver reported by Little and colleagues indicated that 'major' resistance was present in 4%, including nRTI resistance in 3%, NNRTI resistance in 1%, and protease inhibitor resistance in 3%. Any level of reduced susceptibility was present in 14%, including 3% to nRTI, 14% to NNRTI, and 13% to protease inhibitors. However, the threshold for the reduced susceptibility in this survey (called moderate resistance and defined as increases in IC₅₀ of ≥ 2.5 but less than 10-fold) requires careful assessment as to whether this represents a predictor of therapeutic response (eg, isolates with 4- or 5-fold elevated IC₅₀ values for NNRTIs, compared with the 500- or 1000-fold increases indicative of clinically significant resistance). Most of the cases of reduced susceptibility of moderate levels were associated with genetic polymorphisms (variants seen in untreated patients) rather than with primary resistance mutations. Another study, conducted by Wegner and colleagues at the Walter Reed Army Institute for Research (WRAIR), assessed

genotype and phenotype in 114 patients with documented seroconversion within 3 years. In the WRAIR study intermediate resistance and high-level resistance were defined as IC₅₀ increases of ≥ 5 fold and >10 fold, respectively. Resistant genotypes and phenotypes were found in 4% and 7%, respectively, for nRTIs; 15% and 20%, respectively, for NNRTIs, and 10% and 1%, respectively, for protease inhibitors. Most isolates were resistant to only 1 class of drug; 2% to 3% exhibited multidrug resistance.

USE OF DRUG RESISTANCE TESTING WHEN CHANGING THERAPY

A confirmed significant increase in plasma HIV-1 RNA level should remain the main trigger for considering a change in antiretroviral therapy due to drug failure. Resistance testing might be used as a complement to a thorough treatment history in selecting a new regimen. If resistance to a drug has ever been detected in a patient, those resistant mutants may persist as a minority viral pool; thus, regardless of a subsequent finding of susceptibility, that drug should probably not be used again unless no other options are available. Currently, resistance testing is likely to have greatest utility in cases of treatment initiation in acute HIV-1 infection (to assess for transmission of resistant virus) and in patients experiencing their first or second failure of treatment. Owing to the possibility of persistence of virus resistant to previously used drugs, resistance tests are likely to be much less helpful in the highly antiretroviral experienced patient in whom there are few or no new drug options available.

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VIRAL AND CELLULAR DYNAMICS IN HIV-1 DISEASE

At the Atlanta course, R. Pat Bucy, MD, PhD, discussed viral and cellular dynamics in HIV-1 disease, presenting a number of provocative concepts emerging from recently reported findings of others, as well as from the ongoing work of Dr Bucy's group.

The natural history of HIV-1 disease is considered to be a continuum of progression comprising 3 general phases. The acute infection stage, lasting 2 to 3 months, is characterized by high viral load and an acute flulike illness in some cases. A dramatic decrease in plasma HIV-RNA level (viral load) then occurs coincident with the development of effective CD8+ T-cell response. The clinical "latent" disease stage, lasting from approximately 6 months to more than 20 years, is characterized by wide interindividual variability of viral load but relative stability within the individual, with the viral load being correlated with rate of loss of CD4+ cells. Clinically, this stage is marked by lymphadenopathy and constitutional symptoms. Late-stage disease is characterized by low and more rapidly declining CD4+ count, often accompanied by increased viral load, and onset of opportunistic infections. These phases feature different viral and cellular dynamics; recent findings have contributed to elucidation of these dynamics and have increased appreciation of their potential complexity.

HOST MECHANISMS IN CONTROL OF VIRAL REPLICATION

Of dominant interest have been the host mechanisms of viral control following the increase in viral load in primary infection that determine the steady-state level of viral burden during the prolonged second phase of disease. The primary concept invoked to explain this control is that of antigen-specific immune response. The effector mechanism in this response is considered to be the CD8+ T-cell (cytolytic T-cell), the efficiency of which may be determined or modulated by HIV-1-antigen-specific CD4+ T-cell activity,

Although numerous in vitro studies have shown an association of cytolytic T-cell activity with viral replication, only very recently reported studies in simian immunodeficiency virus-infected animals have shown that in vivo depletion of CD8+ T cells results in increased viral load. Evidence for an antigen-driven immune response as the mechanism of viral control is also provided by data indicating a relationship between particular alleles

Potent antiretroviral therapy results in a decrease in CD8+ T-cell effector activity in association with decreased levels of viral antigen

of MHC class I antigens (which serve as antigen-presenting cell elements for CD8+ T cells) and both viral load during early infection and rate of disease progression. Finally, it has been shown that initiation of potent antiretroviral therapy results in a decrease in CD8+ T-cell effector activity in association with decreased levels of viral antigen. Similarly, if cessation of such therapy results in viral rebound, CD8+ T-cell activity subsequently increases.

Another potential host mechanism of viral control is the availability of CD4+ T cells for viral infection. In this concept, replication is controlled by the limited number of available activated CD4+ cells, with the variance in steady-state viral replication among individuals being determined by interindividual variance in availability of these cells. This concept is supported by mathematical models and by

the observation that viral load increases with immune activation by immunization or interleukin-2 (IL-2) administration. However, although this mechanism may contribute to the level of the viral load set point during relative steady state, the possibility that it is not a primary mechanism is suggested by a number of findings. One is that the approximately 5-log variability observed in viral load during this period does not appear to be accounted for by differences in availability of CD4+ T cells (which may exhibit a 3-fold interindividual variability). Another is that studies in lymph node tissue indicate that the absolute frequency of activated T cells is approximately 100- to 1000-fold higher than the frequency of HIV-1-infected T cells. This large excess of apparently available target cells may argue against availability of activated CD4+ cells as a limiting factor in viral load. However, it should be noted that the factors that determine what defines a susceptible activated CD4+ cell remains unclear; even in vitro, not all activated CD4+ cells are target cells for the virus.

EFFECT OF POTENT ANTIRETROVIRAL THERAPY INDUCTION ON VIRAL AND CELLULAR DYNAMICS

Observation of viral and cellular dynamics after initiation of potent antiretroviral therapy has provided additional information on the interaction of viral and cellular factors. Initiation of potent antiretroviral therapy typically results in rapid decline in the plasma HIV RNA level, characterized by an exponential decay with an apparent half-life of 1 to 2 days (Figure 1); this initial rate of decline is consistent among individuals and independent of initial absolute viral load. After 1 to 2 weeks, the rate of decline slows to what has been termed the second-phase decline. The decrease in viral load reflects not only a decrease in circulating virus but also a decrease in HIV RNA-positive cells in lymphoid tissue, suggesting that the plasma HIV-1 RNA level reflects whole-body viral burden (Figure 2).

Along with the rapid reduction in viral load, there is a rapid increase in

CD4+ cells in the blood. The increase appears to occur in 2 phases, a phase of rapid increase over 4 to 6 weeks and a slower phase possibly lasting for months to years. The first phase comprises a nonspecific increase in total lymphocyte count, including increases in CD4+ and CD8+ T cells and B cells, whereas the second phase may more specifically involve CD4+ T cells. Use of a new assay has shown that thymic output of new cells persists even into late life, though at attenuated levels. According to Dr Bucy, whereas there are alternative mechanisms that may explain the initial increase in total lymphocyte count, the second phase of CD4+ increase may represent a combination of expansion of existing cells and thymic generation of new cells. Particularly during the initial-phase CD4+ cell increase, there appears to be significant functional immune reconstitution, as evidenced by the acute marked reduction in constitutional symptoms. The improved immune function is subsequently associated with reductions in such clinical events as new opportunistic infections and death.

One model that was proposed to explain the CD4+ cell increase suggested that the cessation of viral replication after the initiation of potent antiretroviral therapy results in a rapid reduction in CD4+ cell death. In the context of the steady state

high viral replication and clearance in which CD4+ cell death and production are at high flux equilibrium, the increased CD4+ cell production does not cease coincident with the reduction in virus-mediated cell death, resulting in a rapid rise in the CD4+ cell population. Some of the observations of cell numbers are not consistent

with this model, like the increases in CD8+ cells and B cells observed during the phase of CD4+ cell increase. However, more recent findings, like the identification of the second-phase increase in CD4+ cell number, have resulted in a more complex picture of the CD4+ cell dynamics under antiretroviral therapy. T cells and other lymphoid cells sequestered in lymphoid tissue (eg, via increased adhesion molecule expression resulting from virus-mediated immune activation) are redistributed into the circulation upon the relief of tissue inflammation resulting from the reduction in viral antigen levels under therapy. This redistribution may account for much of the early change in CD4+ cell count. However, it is likely that increases resulting from decreased cell destruction and increased cell production, including thymic production, also begin with the suppression of viral burden upon treatment induction, with these continuing changes being identified as the second-phase increase once the early rapid rise has stabilized. The functional immune reconstitution observed may result from restoration of a more normal, less 'activated,' lymphocyte population that is consequently more functional, from the generation of new cells occurring continuously from the time at which viral load is suppressed, or from some combination of these, and perhaps other, factors.

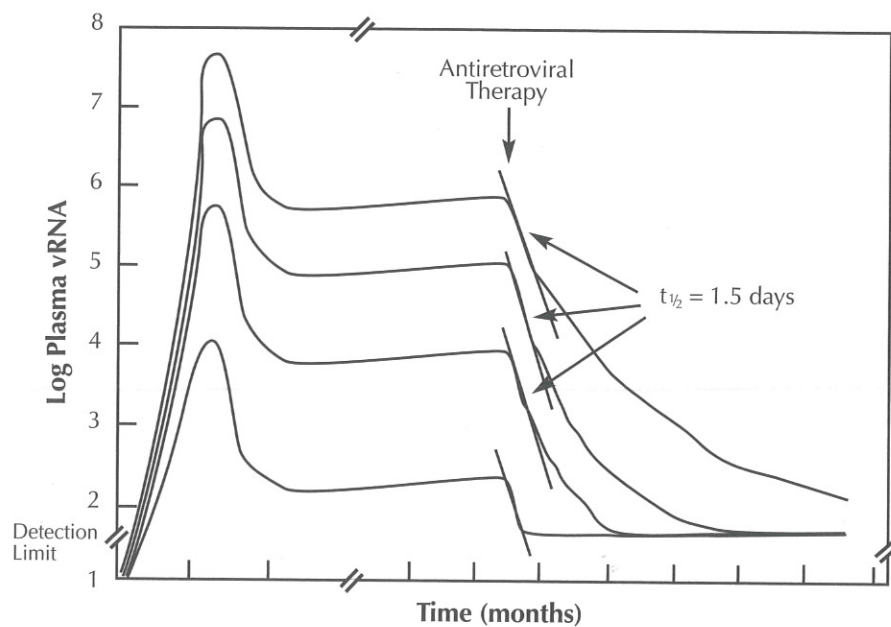


Figure 1. Idealized representation of effect of potent antiretroviral therapy initiation on viral load in 4 cases characterized by relative steady-state viral loads of different magnitudes. Straight lines indicate the slope of the initial decrease in viral load after treatment is started.

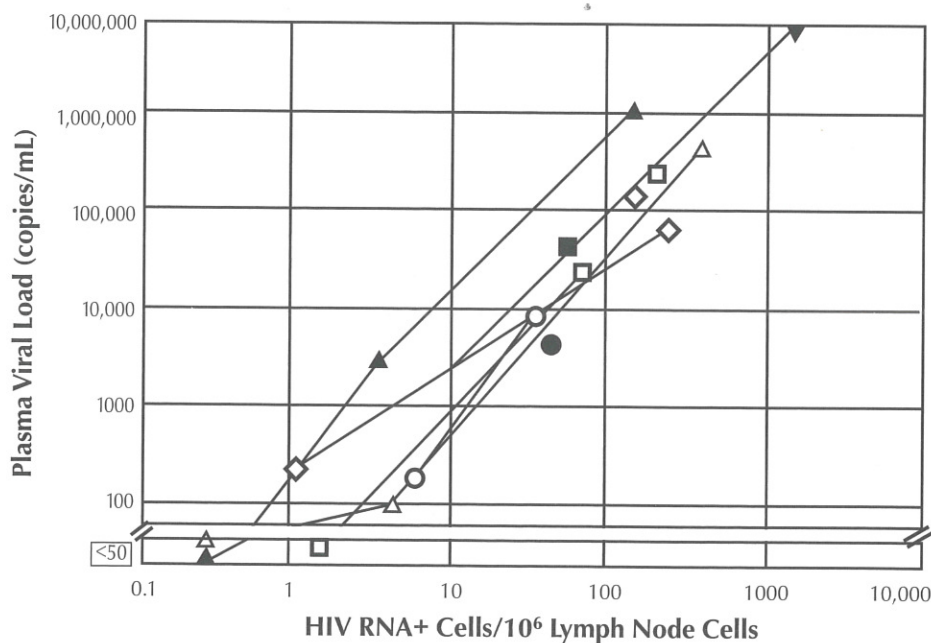


Figure 2. Correlation of plasma HIV-1 RNA level with RNA-positive cells in lymph nodes. Adapted with permission from Hockett RD et al. *J Exp Med.* 1999;189:1545-1554. Copyright 1999, The Rockefeller University Press.

VIRAL DYNAMICS DURING POTENT ANTIRETROVIRAL THERAPY

Despite initial optimism, it is clear that viral infection is not eradicated with potent antiretroviral therapy, as demonstrated by the viral rebound typically observed upon withdrawal of treatment. A number of pools of residual viable virus have been identified or posited. One reservoir that has been demonstrated to exist consists of latently infected CD4+ T cells, with there also being the possibility that virus persists at sequestered anatomic sites, such as the central nervous system. It has also been suggested that virus remaining at nonsequestered sites is capable of persistent rounds of very low level de novo infection, a process that would be supported by likely intermittent nonadherence to potent antiretroviral therapy regimens. Supporting the idea of persistent viral replication are the findings of a slow evolution of viral quasi species sequences and a low rate of drug resistance mutations even under conditions of stringent adherence to treatment regimens. As pointed out by Dr Bucy, HIV-1 RNA levels below the limit of detection of 50 copies/mL for current highly sensitive assays do not ensure absence of replication: although there is a lack of consensus among investigators on this issue, one set of assumptions indicates that there could be as many as 100,000 replication-active cells producing virus at undetectable levels among an estimated whole body population of 10^{11} lymph node cells (Figure 3).

Potential viral reservoirs include latently infected CD4+ cells, sequestered anatomic sites, and a pool of virus capable of persistent rounds of low-level de novo infection

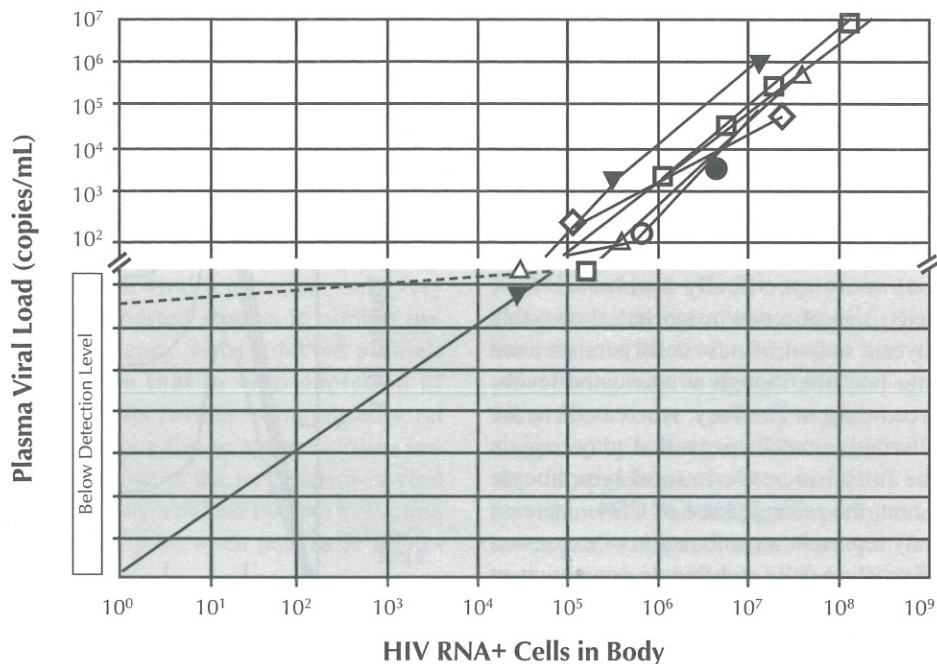


Figure 3. Potential numbers of HIV-1 RNA-positive cells in the body that could still result in plasma HIV-1 RNA level below 50 copies/mL, based on correlation of plasma HIV-1 RNA level and RNA-positive cells in lymph nodes and assumption of 10^{11} lymph node cells in the body. Adapted with permission from Hockett RD et al. *J Exp Med.* 1999;189:1545–1554. Copyright 1999, The Rockefeller Press.

With regard to the pool of latently infected CD4+ T cells that persists despite potent antiretroviral therapy, some groups have found that there is no apparent decrease in frequency of these cells over time in patients started on therapy during chronic infection. The half-life for turnover of these cells has been revised upward with ongoing follow-up of study patients, with current estimates of more than 20 months indicating that a period of 25 to 30 years would be required for this population of cells to be eliminated by natural turnover. One group, however, has identified a more rapid decrease in frequency of these cells, with a half-life of approximately 6 months, in patients started on potent antiretroviral therapy in early infection. In addition, another group has reported clearance of latent infection with IL-2 treatment in 2 patients followed up for a short period. In addition to the identification of latently infected CD4+ T cells, HIV-1 RNA can be detected in lymphoid cells despite its being undetectable in plasma, with viral RNA having been identified in peripheral blood monocytes, lymph nodes, gut mucosa, semen, and cerebrospinal fluid. Dr Bucy stated that it is likely that this apparent ongoing replication accounts for the rebound in viral levels upon withdrawal

of treatment. Although these viral RNA-expressing cells may arise from persistent rounds of de novo cellular infection, an alternative concept is that these rare cells arise from activated latently-infected cells that do not initiate new rounds of infection under continuing therapeutic drug concentrations.

Although most anecdotal reports of withdrawal of potent antiretroviral therapy have indicated a rapid rebound in viral load with treatment withdrawal, there have been a few highly publicized recent reports of delay or absence of rebound in patients in whom treatment was started in early infection. It is hypothesized that preservation of immune response through early potent treatment in these patients permits control of infection once treatment is stopped. One group has reported that viral rebound in patients stopping treatment was accompanied by increased cytolytic T-cell response; in 2 of 4 patients, viral load subsequently returned to and has remained at levels below detection, with 1 patient having been followed up for 23 months.

Intriguing implications are raised by the combined evidence that (1) immune response controls viral load; (2) early treatment preserves immune response (including

potentially accounting for delayed viral rebound with withdrawal of treatment); and (3) effector immune response is decreased with the reduction in viral antigen resulting from potent antiretroviral therapy. The decreased effector immune response observed with profound viral inhibition permits the persistence of low-level viral replication under potent antiretroviral therapy. One possibility in this regard is that latently infected cells that become activated are permitted to revert to a latent

phenotype owing to slowing or absence of clearance by CD8+ T cells. This scenario suggests the potential for using therapeutic immunization or similar methods to induce an active immune response as an adjunct to potent antiretroviral therapy. Most studies of therapeutic immunization were performed prior to the use of profoundly suppressive antiretroviral therapy—ie, in patients who still harbored significant amounts of viral antigen. Antigenic stimulation of the effector immune

response by a therapeutic vaccine in patients receiving potent antiretroviral therapy merits investigation to determine if it can prevent persistent replication attributable to loss of this response through absence of antigen.



R. Pat Bucy, MD, PhD, is Associate Professor of Pathology at the University of Alabama at Birmingham.

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STRATEGIES FOR TREATMENT AND MANAGEMENT OF ANTIRETROVIRAL FAILURES

At the New York course, Scott M. Hammer, MD, discussed strategies for maintaining antiretroviral responses achieved with potent induction antiretroviral therapy as well as strategies for managing suboptimal response or antiretroviral failure.

The current standard of antiretroviral therapy in the clinical setting is to begin treatment with a potent regimen to suppress plasma viral load below limits of detection of sensitive assays and to maintain as potent a regimen as possible with routine monitoring of clinical status, plasma HIV-1 RNA, and CD4+ cell count. Treatment with a protease inhibitor and 2 nucleoside reverse transcriptase inhibitors (nRTIs) has proven effective in initial therapy and is commonly used; however, there are a number of other options for the initial regimen treatment, including a nonnucleoside reverse transcriptase inhibitor (NNRTI) plus 2 nRTIs, 2 protease inhibitors plus 1 or 2 nRTIs, a protease inhibitor/NNRTI/nRTI(s) combination, and a triple-nRTI combination. Despite the large number of drugs currently available and the ability to combine them effectively in initial treatment, cross-resistance among drugs in particular classes—and decreased effectiveness even in the absence of genotypic evidence of cross-resistance—results in numerous difficulties in managing patients in whom there is a suboptimal response to the initial therapy, a subsequent treatment failure, or prior extensive exposure to available drug classes. A number of strategies have begun to be formulated to optimize management in this regard.

INDUCTION–MAINTENANCE STRATEGIES

After profound suppression of viral burden has been achieved with therapy, the rationale for use of a maintenance regimen is that a simplified regimen might maintain suppression in the context of a reduced infected cell reservoir. However, this approach has proven unsatisfactory

The rationale for use of a maintenance regimen is that a simplified regimen might maintain suppression in the context of a reduced infected cell reservoir

with maintenance regimens evaluated to date in clinical trials (Table 1). In ACTG 343, patients receiving zidovudine/lamivudine/indinavir who had plasma HIV-1 RNA levels below 200 copies/mL at 24 weeks were randomized to continued treatment with the triple regimen, zidovudine/lamivudine, or indinavir alone. In the Trilege study, patients receiving the same triple combination who had plasma HIV-1 RNA levels below 500 copies/mL at 12

weeks were randomized to continued triple-drug treatment, zidovudine/lamivudine, or zidovudine/indinavir. In the ADAM trial, patients receiving stavudine/lamivudine/nelfinavir/saquinavir with viral load below 50 copies/mL at 26 weeks were randomized to continuation of the 4-drug regimen, stavudine/nelfinavir, or nelfinavir/saquinavir. In each of these trials, failure rates were markedly higher in patients receiving the simplified maintenance regimens. These disappointing findings, however, do not indicate the lack of viability of such an approach; they more likely suggest the need for more prolonged or potent induction treatment and/or more potent maintenance regimens.

“SWITCHING” THERAPY

Change from a potent induction regimen to another potent regimen may be advantageous to avoid or ameliorate toxic effects, despite continued suppression of viral load with the induction regimen. In the case of protease inhibitor toxicity, for example, an NNRTI/dual nRTI or triple nRTI regimen could be substituted for a protease inhibitor/dual nRTI regimen. Although the

Table 1. SUMMARY OF RESULTS OF INDUCTION–MAINTENANCE TRIALS

Study	Induction Therapy	Maintenance Therapy	Failure Rate (%)
ACTG 343 (Havir et al. <i>N Engl J Med</i> , 1998)	Zidovudine/lamivudine/ indinavir	Zidovudine/lamivudine/ indinavir	4
		Zidovudine/lamivudine	23
		Indinavir	23
Trilege (Pialoux et al. <i>N Engl J Med</i> , 1998)	Zidovudine/lamivudine/ indinavir	Zidovudine/lamivudine/ indinavir	9
		Zidovudine/lamivudine	31
		Zidovudine/indinavir	22
ADAM (Reijers et al. <i>Lancet</i> , 1998)	Stavudine/lamivudine/ nelfinavir/ saquinavir	Stavudine/lamivudine/ nelfinavir/saquinavir	9
		Stavudine/nelfinavir	57
		Nelfinavir/saquinavir	71

number of drugs in the regimen may be unchanged, a potential benefit of switching may be simplification of the dosing regimen or reduction in total pill burden. A preliminary report by Ruiz and colleagues of the Spanish Lipodystrophy Study Group has indicated favorable early outcomes using this strategy in patients with lipodystrophy who were taking protease inhibitor-containing regimens. The target population was 100 patients who had received stavudine/lamivudine/protease inhibitor for at least 9 months, had plasma HIV-1 RNA levels below 400 copies/mL for at least 6 months, and who had protease inhibitor-associated lipodystrophy. The patients were randomized to continue treatment with their protease inhibitor-containing regimen or to predominantly change to stavudine/didanosine/nevirapine for 1 year; didanosine was substituted for lamivudine in the nevirapine-containing arm in order to avoid lamivudine resistance in case virologic failure occurred in the nevirapine group. In 29 patients in whom 12-week data were available, duration of prior protease inhibitor therapy was nearly 2 years, with viral suppression for 14 to 17 months and CD4+ cell counts greater than 500/ μ L. The 12-week data indicated that patients who switched to the nevirapine-containing regimen had significant decreases in cholesterol and triglyceride levels and significant improvement in subjective quality of life and physician and patient qualitative estimates of lipodystrophy. The CD4+ cell counts remained stable and plasma HIV-1 RNA levels generally remained below 50 copies/mL in both patient groups. A trend towards improvement in objective measures of lipodystrophy was observed in patients receiving the nevirapine-containing regimen, although changes did not achieve statistical significance. These data are preliminary, although they do suggest the ability to maintain virologic benefit and improve metabolic aspects of lipodystrophy over at least the short term by switching drug regimens. Additional data with longer follow-up time are needed.

INTENSIFICATION

Intensification of treatment can consist of adding a drug to a regimen if initial response is good but not optimal, or adding a

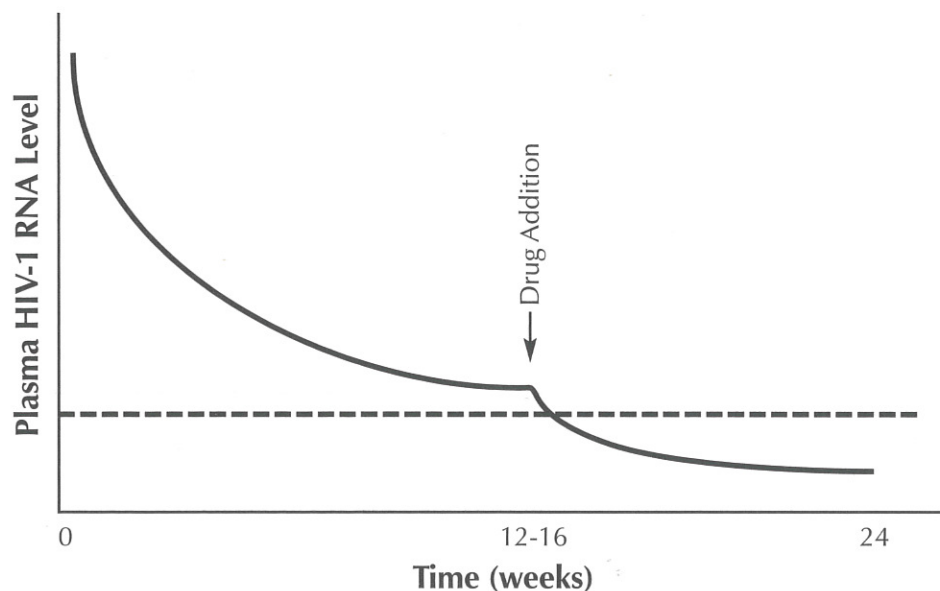


Figure 1. Example of good but suboptimal virologic response to induction therapy, in which slope of plasma HIV-1 RNA decrease indicates plateauing of effect before assay limit of detectability (dotted line) is achieved. The rationale in regimen intensification in such cases is to achieve a viral load below the level of detection with the objective of preventing the emergence of drug resistance and producing a durable response.

drug to an already successful regimen to promote durability of response. The latter approach currently is being investigated in ACTG 372. In this study, patients from ACTG 320 who received zidovudine/lamivudine/indinavir and in whom plasma HIV-1 RNA levels were maintained below 500 copies/mL were randomized to addition of abacavir or placebo to determine if the addition of the active drug could prolong the time to virologic failure. The former approach has been considered in cases in which the effect of a regimen in reducing viral load appears to be reaching a plateau, resulting in persistently detectable plasma HIV-1 RNA levels (Figure 1). In such cases, the addition of a drug at, for example, 12 to 16 weeks may achieve and maintain the desired additional reduction in viral load. There is some evidence from clinical trials that this approach may be of benefit. For example, in the initial ritonavir/saquinavir trial sponsored by Abbott Laboratories, the addition of stavudine/lamivudine or other nRTIs in patients in whom the initial therapy failed to achieve HIV-1 RNA levels below 200 copies/mL by week 12 resulted in maintained suppression for 60 weeks in the majority of cases. Similarly, in the Glaxo Wellcome 3003 trial, the addition of abacavir in patients receiving dual nRTI therapy resulted in durable responses through 48 weeks.

Issues to be addressed with regard to treatment intensification include timing of intervention and whether frequency of plasma HIV-1 RNA monitoring should be increased during initial treatment to allow earliest appropriate intervention. In addition, there is a fine line between intensification and incremental therapy in the setting of early virologic failure. The latter is to be avoided as further drug resistance may be promoted. With regard to which class(es) of drug to use in intensification, those with a low genetic barrier to resistance (eg, an NNRTI or lamivudine) would be less ideal. Those requiring multiple mutations for resistance (eg, abacavir) may be more appropriate.

MANAGEMENT OF ANTIRETROVIRAL FAILURE

Although antiretroviral failure can be defined clinically and immunologically, the most sensitive marker for failure currently available is a confirmed change in plasma HIV-1 RNA level. The differentiation of suboptimal response to induction treatment from early viral rebound due to regimen failure is a consideration in deciding whether to switch treatments based on virologic findings. The former might motivate regimen intensification, whereas the latter motivates early treatment of virologic

breakthrough. As part of routine clinical practice, other potential causes for decreased virologic effect—including poor drug absorption, lack of adherence, intercurrent illness, and immunization—should be investigated prior to intervention. An additional consideration in treatment change is the viral load threshold for inter-

A recently recognized issue in switching regimens based on early virologic failure of protease inhibitor-, lamivudine-containing regimens is whether all drugs in the regimen need to be changed

vention—ie, should any confirmed viral load using the most sensitive assays available trigger a change in treatment or should a higher threshold be used as a more practical approach. Many clinicians would accept any confirmed detectable virus as a trigger for changing therapy in the first occurrence of virologic failure. However, with fewer treatment options after subsequent failures, acceptance of a higher threshold might be required. This practice may be easier to rationalize given, for example, the fact that the CD4+ cell count often remains elevated for prolonged periods after protease inhibitor failure. In short, with currently available treatment options, it remains an issue whether rigorous pursuit of the standard of maintaining plasma HIV RNA levels below limits of detection after initial drug failure will result in the most durable responses in the long term or result in the earlier narrowing or exhaustion of subsequent treatment options.

A major issue in switching regimens based on virologic failure is whether all drugs in the regimen need to be changed.

Although current practice generally reflects the belief that total replacement of a failing regimen is warranted to avoid incremental therapy, recent data indicate that earliest failures in protease inhibitor/zidovudine/lamivudine regimens are associated with the codon 184 lamivudine-associated resistance mutation and an absence of protease inhibitor-associated mutations. In a group of 17 patients from ACTG 343 with viral rebound during indinavir/zidovudine/lamivudine therapy (means of 45 weeks on therapy and 25 weeks of viral rebound, and mean plasma HIV-1 RNA level of 27,819 copies/mL during rebound), indinavir and lamivudine phenotypic resistance was found in isolates from 0 and 14 patients, respectively, with the M46L protease mutation being found in 1 case and the lamivudine-associated M184V mutation being found in 14. Similar findings have been reported in the Trilege study and in the ACTG 347 study of amprenavir-containing triple therapy. At present, however, it is unclear how to integrate such information into clinical practice. Although resistance testing is likely to ultimately prove useful in guiding selective changes in combination regimens, current phenotypic and genotypic tests are subject to limitations, including the failure to detect minority resistance populations. Currently, then, changing only 1 component of a failing regimen would warrant particularly close monitoring for virologic response. Overall, it would appear to be prudent to change most if not all components of a failing regimen to avoid the potential consequences of incremental therapy until it is clearer how to integrate information on component failure into clinical practice.

A number of largely nonrandomized studies of salvage therapy after protease inhibitor failure have been reported over the past year. In a representative study (Glaxo Wellcome, CNA 2007), highly antiretroviral-experienced patients (including many patients with multiple protease inhibitor experience and multiple nRTI and/or NNRTI experience) in whom a protease inhibitor-containing regimen failed, were given the combination of abacavir/amprenavir/efavirenz. Those patients with baseline viral load levels 40,000 copies/mL or below who were NNRTI-naïve had a good initial response with maintenance of a 1-log reduction in

viral load at 16 weeks. Initial responses were poorer in NNRTI-experienced patients, particularly in those with higher baseline viral loads. Only 5% of NNRTI-experienced patients with baseline viral loads greater than 40,000 copies/mL had viral loads below 400 copies/mL at week 16, compared with approximately 50% of NNRTI-naïve patients with baseline viral loads below 40,000 copies/mL. Similar findings have been observed in other studies. Response rates at 16 to 24 weeks have ranged from 5% to 70%, with better rates of response noted when a change in treatment was initiated at lower rather than higher viral loads.

There are considerable uncertainties about what regimen to use after failure of a protease inhibitor-containing regimen. The current knowledge of potential therapeutic options in the cases of prior protease inhibitor exposure can be summarized as fol-

Overall, it would appear prudent to change most if not all components of a failing regimen to avoid the potential consequences of incremental therapy

lows: With regard to alternative protease inhibitors, (1) the response to indinavir or nelfinavir following saquinavir is blunted, indicating that the common saquinavir-associated L90M resistance mutation confers some degree of cross-resistance to other protease inhibitors; (2) the response to ritonavir/saquinavir in cases of failure on other protease inhibitors is no better than 50% to 70%; (3) based on preliminary clinical data, nelfinavir failure is associated with variable response to other protease inhibitors. Although the signature D30N nelfinavir-associated resistance mutation alone does not appear to confer cross-resistance to other protease inhibitors, the

addition of other mutations to the codon 30 mutation does result in cross-resistance; (4) the amprenavir-associated I50V resistance mutation does not by itself cause protease inhibitor cross-resistance, but other mutations that do, commonly occur in the setting of amprenavir-failure; and (5) it is unclear what role amprenavir may have in salvage treatment.

With regard to NNRTIs, although replacement of a protease inhibitor-containing regimen with a NNRTI/dual nRTI regimen has been commonly advocated and employed, prior nRTI exposure compromises the effectiveness of such regimens. This is of particular importance for NNRTIs, since these drugs are subject to one-step, high-level resistance, and the potency of the overall combination is crucial to preventing rapid emergence of NNRTI resistance.

With regard to nRTIs, the potential compromise of response due to prior nRTI exposure must be considered a factor rendered more complicated by the fact that this decreased effectiveness is not always explained by known mutations conferring cross-resistance. Abacavir, which has been found to be a potent component of initial therapy, may have some promise for use in cases of first virologic failure, particularly since it retains reasonable activity against lamivudine-resistant virus. However, since the presence of multiple nRTI resistance mutations is associated with abacavir resistance, the use of abacavir in subsequent failures in highly nRTI-experienced patients is less efficacious.

Although the acyclic nucleotide reverse transcriptase inhibitor (nRTI), adefovir dipivoxil, has only modest intrinsic activity, it may have a role in subsequent therapy, particularly since it has shown activity against lamivudine-resistant virus.

Hydroxyurea is currently being used as an adjunct in alternative antiretroviral regimens, with the majority of experience with the drug in combination with didanosine or didanosine/stavudine. These combinations have been associated with good virologic response usually accompanied by lack of change or a decrease in CD4+ cell count. There are some data to indicate that delayed introduction of hydroxyurea with the alternative regimen may improve

Treatment after the initial regimens fail remains largely an empiric choice involving as many new drugs as possible (eg, dual protease inhibitors plus nRTIs with or without an NNRTI)

the CD4+ cell response but this requires further study. An advantage of hydroxyurea is its apparent ability to preserve didanosine activity against didanosine-resistant mutants. Its utility with other nRTIs or nucleotide reverse transcriptase inhibitors (nRTIs) remains to be fully defined.

Based on these considerations, treatment after the initial regimen(s) fail remains largely an empiric choice involving as many new drugs as possible (eg, dual protease inhibitors plus nRTIs with or without an NNRTI). Data from controlled clinical trials are urgently needed to identify successful regimens and to define the potential role of resistance testing in guiding treatment changes. It is also clear that new drugs are needed to devise regimens that are active against multidrug-resistant virus.

STRATEGIC MANAGEMENT

Dr. Hammer proposed a general strategy for antiretroviral management reflecting the above considerations. (1) Initiate therapy with a potent combination to drive plasma HIV-1 RNA level below the limit of detection, using the most sensitive available assays as part of routine clinical care. (2) Monitor plasma HIV-1 RNA level at 4, 16, and 24 weeks at the mini-

um, with more frequent early monitoring potentially being useful. In the case of an excellent response, treatment should be continued. In the case of good but suboptimal response, intensification or a change of regimen should be considered. It is important to note that with use of sensitive viral load assays, which have detection limits of 20 to 50 HIV-1 RNA copies/mL, the time to achieve viral loads below the levels of detection may be greater than 16 weeks (and may be as long as 32 weeks, although a delay of this amount of time may suggest possible adherence problems); thus, with use of such assays, monitoring the trajectory of decline in viral load is important. (3) Virologic monitoring should continue on a routine basis once plasma HIV-1 RNA level has been reduced to levels below detection; although 3-month intervals have been widely used, many clinicians now monitor more frequently (eg, every 2 months) to detect failure more promptly. (4) If plasma HIV-1 RNA becomes detectable, all potential reasons for drug failure should be evaluated, including nonadherence, poor drug absorption, intercurrent illness, and vaccination. If drug failure is evident or considered likely, changing the regimen at a lower plasma HIV-1 RNA level is more likely to be successful than delaying intervention until viral load is higher—although practical concerns may dictate otherwise. (5) The same principles apply in the case of failure of a second regimen; however, given the cumulative limitation of options, compromise is frequently necessary. (6) The current role of resistance testing in clinical decision-making is unclear, although it is likely to prove useful in the future. Thus, the importance of provider expertise in antiretroviral therapy decision-making will continue to increase.

Scott M. Hammer, MD, is Chief of the Division of Infectious Diseases at Columbia-Presbyterian Medical Center and Professor of Medicine at Columbia University College of Physicians and Surgeons, New York, New York.

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Courtesy Announcement

AIDS Knowledge Base
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<http://hivinsite.ucsf.edu>

Coming soon: HIV InSite and the International AIDS Society—USA will jointly present clinical cases on the web, online CME courses

HIV InSite is not affiliated with the International AIDS Society—USA.

RENAL COMPLICATIONS IN HIV DISEASE

At the New York course in fall 1998, Paul E. Klotman, MD, presented two cases of renal disorders in individuals with HIV disease. The first, concerning HIV-associated nephropathy, was summarized in the December 1998 issue of this publication. The details of the second case presentation are summarized below, followed by a discussion of diagnosis and management.

CASE DESCRIPTION

PRESENTATION:

A 28-year-old white woman, HIV-seropositive for 8 years with a history of *Pneumocystis carinii* pneumonia presented to the emergency room with shortness of breath. Her CD4+ cell count was 200/ μ L; plasma HIV RNA level was 1.8×10^4 /mL. The patient was antiretroviral-experienced with presumed drug-resistant viral strains. She began taking the investigational antiretroviral drug adefovir through the expanded access program at a dose of 120 mg/d 30 weeks prior to coming to the emergency room. She had responded with a 1-log decrease in her plasma HIV RNA level and an increase in her CD4+ cell count to 220/ μ L.

PHYSICAL FINDINGS

4-lb weight loss
Afebrile
Respiratory rate of 25
Pulse, 64 bpm
Blood pressure, 124/82 mm Hg
Rhonchi that cleared with coughing
Cardiovascular exam findings were normal

LABORATORY FINDINGS

Na⁺: 135, Cl⁻: 115, K⁺: 3.2, and
HCO₃⁻: 14 mEq/L
Creatinine: 1.5 mg% (6 months prior
it was 1.3 mg%)
Urinalysis: urine pH: 5, glucose 1+,
protein 2+, no cellular sediment
White blood cell count: 5000/ μ L
Chest X-ray: increased interstitial markings but no change from before

DIAGNOSIS

The patient's respiratory rate was clearly increased raising the possibility of a primary pulmonary problem or an acid-base disorder. The low bicarbonate and the absence of an anion gap are suggestive of metabolic acidosis, but the blood gas was required to sort out a primary from a secondary disorder. The pH defined the problem as primarily an acidosis (nephrologists often refer to this as an acidemia) that represents a mixed acid-base disorder: a primary metabolic acidosis with a compensating respiratory alkalosis. Thus, the high respiratory rate is appropriate for the underlying metabolic disorder. The acid-base disorder was not recognized, however, and the patient underwent a ventilation perfusion scan (low probability for embolic disease) followed by bronchoscopy and lavage for *Pneumocystis carinii* (which was negative). Had the

metabolic disorder been recognized, these tests could have been avoided.

Additional chemistries revealed the following: glucose 102 mg/dL, blood urea nitrogen 22 mg/dL, phosphate 1.2 mg/dL, calcium 8.5 mg/dL, uric acid 6.2 mg/dL, and alkaline phosphatase 346 U/L (normal range, 30–110). Because she had an elevated creatinine and a profound acidosis, a 24-hour urine collection was obtained and showed a creatinine clearance of 60 mL/min and a protein excretion 1.5 gm/24 hour. Liver function tests were normal. After reviewing these tests, it was apparent that the patient had experienced a decline in renal function associated with the development of a non-anion gap acidosis. The overall renal functional impairment was not sufficient to account for the profound loss of bicarbonate, and the absence of cellular elements in the urine suggested that this was not an allergic interstitial nephritis. '

The presence of what appears to be a renal tubular acidosis with glycosuria and possibly phosphaturia strongly suggests a Fanconi syndrome. Fanconi syndrome is a combination of a type II or proximal renal tubular acidosis with general tubular dysfunction that is characterized by hyperchloremic non-anion gap metabolic acidosis. Tubular acidoses are often accompanied by hypokalemia as well. Under normal conditions, the proximal tubule reabsorbs 85% of the filtered load of bicarbonate through carbonic anhydrase-mediated resorption. If as a result of injury, toxicity, or an inherited defect the proximal tubule cannot manage the filtered load, then bicarbonate (and sodium) is delivered to the distal tubule where the capacity to reabsorb bicarbonate is low. Thus, urine pH rises as bicarbonate and sodium (and potassium as well) are lost in the urine. Eventually the filtered load of bicarbonate is reduced and the dysfunctional proximal tubule, even with its diminished capacity for reabsorption, can once again resorb 85% of the diminished amount of bicarbonate that appears in the filtrate. At this point, the distal nephron can deal with the remaining bicarbonate and urine pH falls in the face of a metabolic acidosis. As a result, one of the hallmarks of proximal renal tubular acidosis is the ability to excrete an acid urine when serum bicarbonate is sufficiently reduced. In contrast, a distal renal tubular acidosis does not allow effective urinary acidification because the proton gradient cannot be maintained in the distal nephron and any hydrogen gradient is quickly dissipated. In distal renal tubular acidosis, an acid urine is almost never generated.

The patient presented here was receiving adefovir and the most likely diagnosis, then, is adefovir nephrotoxicity manifested by a Fanconi-like syndrome and a reduction in glomerular filtration rate. The precise mechanism of the nephrotoxicity of adefovir is unknown. Adefovir exhibits low protein binding (<3%) and is excreted unchanged in urine. The drug clearance rate exceeds glomerular filtration rate by 3-fold, suggesting tubular secretion. The mechanism

of transport both into and out of the renal epithelial cell remains unknown but probenecid partially inhibits its excretion. Adefovir nephrotoxicity usually involves the proximal tubule but may involve other segments as well. There is currently no evidence that the glomerulus is affected by adefovir.


The patient had evidence of renal glycosuria, phosphaturia, and an increase in alkaline phosphatase of bone origin, probably as a result of the acidosis and hypophosphatemia. Adefovir toxicity is clearly related to duration of exposure and has been observed in 30% to 49% of patients receiving the 120 mg/d dose for more than 6 months. The toxicity usually resolves with discontinuation of therapy. In a study of 403 patients receiving adefovir at a dose of 120 mg/d, 6% had a serum creatinine concentration that had not returned to baseline and 9% had a serum phosphate concentration less than 2 mg/dL at the end of the study. In all of these patients, the trends of the creatinine and phosphate concentrations have been to return toward baseline. Unfortunately, follow-up is inadequate at this time to demonstrate that all laboratory values return to their initial values following the

discontinuation of the drug. As a result of the frequency in renal toxicity, the current recommendation is that patients receive the 60 mg/d dose.

MANAGEMENT

Management of adefovir toxicity can be accomplished by reducing the dosage by 50% or by discontinuation of the drug if renal parameters do not resolve. In this case, the dose was reduced to 60 mg/d and bicarbonate, potassium, and phosphate supplementation was initiated. For patients who are now initiated on the 60 mg/d dose, the reduction would be to 30 mg/d if toxicity occurred. In general, the treatment of Fanconi syndrome includes maintaining the bicarbonate above 20 mEq/L with sodium bicarbonate or sodium/potassium citrate (3 mEq/kg/d), potassium supplementation to maintain the potassium above 3.2 mEq/L, and supplementing phosphorous with neutral phosphate solutions or oral K-Phos tablets (250 mg phosphate with 4:1 Na⁺:K⁺) if the patient is hypokalemic. Additional vitamin D and phosphorous supplements may be required. The most important parameter to follow is the serum creatinine,

and if the creatinine increases to greater than 0.5 mg% above baseline, adefovir should be discontinued.

The nephrotoxicity clearly limits the duration of use of adefovir in many patients and will impact upon the patients who will likely receive the drug. Its benefits are profound for the experienced patient with drug-resistant HIV-1. The once-daily formulation is also an advantage. The major disadvantage is that as many as 50% of patients may have to change therapy due to nephrotoxicity. The long duration of time required to develop toxicity, however, should allow the physician sufficient time to anticipate and then recognize the problem. In the vast majority of patients, the renal impairment is reversible. In the experienced patient with few other options, adefovir should prove to be a useful addition to the antiretroviral armamentarium as long as physicians are aware of the potential toxic effects of the drug. 

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SUGGESTED READING

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ACTIVITIES OF THE INTERNATIONAL AIDS SOCIETY-USA

BRIDGING CLINICAL RESEARCH AND PATIENT CARE THROUGH QUALITY EDUCATION FOR PHYSICIANS

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.

CLINICAL RECOMMENDATIONS

In the past year the International AIDS Society-USA has published 3 reports on clinical management, including reports on antiretroviral therapy, antiretroviral drug resistance testing, and the role of the ganciclovir intraocular implant for CMV (cytomegalovirus) retinitis in the era of potent antiretroviral therapy. These consensus reports are the products of panels of experts in HIV and AIDS, and their goal has been to provide educational information that will inform and assist the work of clinicians actively involved in the care of people with HIV and AIDS.

The antiretroviral therapy and resistance testing panels are each preparing updates of their recommendations. Following is a list of the current recommendations.

ANTIRETROVIRAL THERAPY GUIDELINES

Carpenter CCJ, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1998: updated recommendations of the International AIDS Society-USA Panel. *JAMA*. 1998;280:78-86.

RESISTANCE TESTING GUIDELINES

Hirsch MS, Conway B, D'Aquila RT, et al. Antiretroviral drug resistance testing in adults with HIV infection: implications for clinical management. *JAMA*. 1998;279:1984-1991.

CMV IMPLANT GUIDELINES

Martin DF, Dunn JP, Davis JL, et al. Use of ganciclovir implant for the treatment of cytomegalovirus retinitis in the era of potent antiretroviral therapy: recommendations of the International AIDS Society-USA Panel. *Am J Ophthalmol*. 1999;127:329-339.

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