CHANGING (CONTINUING) THERAPY

WHEN TO CHANGE

43. How should patients be followed to detect antiretroviral failure? CD4+ only? HIV RNA titers? How often?

Dr Yeni: CD4+ cell counts, plasma HIV RNA levels, and clinical symptoms are all appropriate parameters to follow in patients who are taking antiretroviral drugs. Careful assessment of CD4+ cell counts and plasma HIV RNA levels on a regular basis (every 3 to 4 months) may allow detection of antiretroviral failure before the clinical status deteriorates. Monitoring both the CD4+ cell count and the plasma HIV RNA level is necessary because these two variables are not well correlated and independently predict HIV disease progression.

Dr Hammer: As stated, monitoring a patient to detect failure of antiretroviral therapy should involve periodic assessments of the patient's clinical status, CD4+ cell count, and plasma HIV RNA level (if available). It is hoped that by monitoring the two laboratory parameters, changes in antiretroviral therapy can be made before there is symptomatic clinical deterioration. Since CD4+ cell counts and plasma HIV RNA levels provide complementary information with respect to both the efficacy of a current treatment and prognosis, it is becoming increasingly routine to perform these two tests concurrently. As part of routine monitoring, it is reasonable to assess these parameters every 3 to 4 months; if treatment is changed, a repeat assessment approximately 4 weeks later is also helpful to assess the early in vivo response.

44. If a patient has a stable or rising CD4+ count and undetectable HIV RNA on nucleoside monotherapy (zidovudine or didanosine), would you change treatment anyway?

Dr Yeni: The objective of antiretroviral therapy is to stabilize or increase the CD4+ count and to bring the plasma HIV RNA value to an undetectable level. I would not change a treatment fulfilling these objectives in an asymptomatic patient, if the treatment is well tolerated and well accepted by the patient. However, since such a situation is probably unusual, one should check that viral load is not underestimated in the case of a non–B-HIV-1 strain.

Dr Hammer: For patients who are stable on didanosine monotherapy, particularly if they have undetectable plasma HIV RNA levels, there would be no immediate indication to alter therapy. Didanosine monotherapy has been clearly shown to be superior to zidovudine monotherapy and comparable to the combination of zidovudine/didanosine in both adults (ACTG 175) and children (ACTG 152).

45. I have several patients who have been on zidovudine monotherapy for 3 or 4 years. Their CD4+ counts are around 300 cells/μL (and stable) and they are clinically asymptomatic. Their viral load levels have not been measured. Is a change of therapy recommended?

Dr Hammer: For patients who have been stable on zidovudine monotherapy for 3 to 4 years and have stable CD4+ cell counts, the measurement of the plasma HIV RNA concentration (if available) can be quite helpful. Although zidovudine monotherapy is no longer thought to be the routine standard of care, an individual on such treatment with a very low plasma HIV RNA copy number could be considered to be containing the virus at least for the time being. Such patients could continue to be followed carefully for any clinical or marker (CD4+ cell count or plasma HIV RNA) change that would suggest that an alteration in therapy is appropriate. Alternatively, if a patient on long-term zidovudine monotherapy, despite clinical and CD4+ stability, had an elevated HIV RNA copy number(>5000 copies/mL), a change in therapy should be strongly considered.

Dr Yeni: The answer to this question could depend on the plasma viral load. For a patient with an undetectable plasma HIV RNA level, there is no evidence that changing treatment can result in any benefit, and a careful follow-up should be continued. For a patient with a plasma HIV RNA level greater than 5000 to 10,000 copies/mL, there is evidence of treatment failure, so a new combination regimen should be initiated.

WHAT TO CHANGE TO: GENERAL

46. If a patient is stable on two nucleoside RTIs, can a protease inhibitor be added, or should the RTIs likewise be changed?

Dr Hammer: The therapeutic decision depends in part on the options still open to the patient and physician. In general, it is thought preferable to change to a regimen that contains 2 or 3 new drugs when treatment failure has occurred. Therefore, to maximize the effect of the addition of a protease inhibitor and hopefully to minimize the

potential for the emergence of resistance when a protease inhibitor is added, a change in one or both of the original nucleoside RTIs should also be considered. This, however, may not always be possible in an individual who has had intolerance to multiple agents or experience with all of the currently available nucleoside drugs.

Dr Yeni: If stability refers to CD4+ cell count in an asymptomatic patient, the answer to this question depends on the plasma HIV RNA level because the efficacy of treatment is assessed better by the antiretroviral effect than by the CD4+ cell count changes. In case of an undetectable plasma HIV RNA level, the current nucleoside combination is efficient and the virus is probably still sensitive to the drugs. Adding a protease inhibitor to the regimen should therefore not lead to the rapid emergence of resistance. However, the necessity of adding a new drug to an efficient therapy is not demonstrated. Conversely, a plasma HIV RNA level greater than 5000 to 10,000 copies/mL qualifies for a treatment failure (despite stable CD4+ cell count) and should lead to a change in therapy. In that case, the virus has probably become resistant to the two current nucleosides. Therefore, at least one new nucleoside should be added to the protease inhibitor, if possible.

47. Is there a general protocol to always recommend two new drugs rather than one?

Dr Hammer: There is no "general protocol" to always recommend two new drugs rather than one but this is a consensus that has evolved from the clinical trial experience. For example, in general the initiation of either didanosine or zalcitabine with zidovudine in zidovudine-naive subjects confers a greater clinical benefit than is seen in zidovudine experienced subjects. Also, across numerous studies involving different classes of drugs (NRTIs, NNRTIs, and protease inhibitors) the CD4+ cell and plasma HIV RNA responses are greater and more durable in direct proportion to the number of new drugs introduced to the patient.

Dr Yeni: As noted, there is no "general protocol." This recommendation is based on a rationale and clinical observation. The rationale is that the rate of the development of resistance mutations should be lower in patients with the greatest therapeutic antiretroviral effect as assessed by plasma HIV RNA levels. A greater effect is anticipated with a new combination regimen than with a new monotherapy. The clinical observation is that combination therapy, particularly with protease inhibitors, may delay the emergence of resistance.

However, the general recommendation for two rather than one new drug may be attenuated in specific conditions, taking into account several factors such as the number of new drugs still available for an individual patient, and the possible partial reversion of resistance to zidovudine when adding lamivudine.

48. We heard that one should treat HIV infection as one treats TB. If a patient on 2- or 3-drug regimen shows a rise in viral load, one should add or change to 2 other drugs that should have no possible cross-resistance. Could you comment on that?

Dr Yeni: There is an analogy between tuberculosis and HIV infection, in that both are progressive infectious diseases whose courses cannot be significantly and/or durably altered by single-drug therapy because of resistance. An increase in viral load during combination therapy for HIV disease may be due to resistance to only one, or to all combined drugs. In contrast to *M tuberculosis*, resistance to HIV is difficult to demonstrate in clinical laboratories, and it may be difficult to decide which drug should be changed. Furthermore, adding one new drug may be equivalent to switching to monotherapy in the case of a virus resistant to all drugs currently used. Therefore, changing therapy should consist, when possible, of a switch to a new combination including drugs for which there is no cross-resistance between the new combination and the previous one. A partial exception to this general recommendation is failure during combination therapy including zidovudine: the described interaction between zidovudine and lamivudine may allow one to maintain zidovudine in a lamivudine-containing regimen.

Dr Hammer: The analogy to the treatment of tuberculosis is a helpful one but should not be overstated. It is true from a theoretical perspective and from the clinical trials experience that in the setting of treatment failure, an alteration in the regimen that would introduce at least 2 new drugs would be an appropriate strategy. It is clear that the degree and durability of marker responses to antiretroviral treatment regimens in drug-experienced subjects is proportional to the number of new drugs introduced. However, it must be realized that in clinical practice the options are still limited, and this strategy may not always be possible.

49. For patients who are taking zidovudine/lamivudine and who either show a rising viral load and a steady or declining CD4+ count, what would you recommend?

Dr Yeni: In the case of treatment failure with zidovudine/lamivudine, the best option is to switch to another combination regimen. Adequate drugs to be considered are didanosine, stavudine, and protease inhibitors, as stated in the *Guidelines*. However, NNRTIs may also be an option. The number and types of drugs to combine depend on several factors, including the disease stage. Protease inhibitors and 3-drug combinations may be appropriate for patients with advanced HIV disease.

50. For a patient on zidovudine/lamivudine in whom HIV RNA rises, should only a protease inhibitor be added, or should 2 new non-protease inhibiting drugs be introduced? (ie, is anything lost by delaying the protease inhibitor)

Dr Carpenter: The objective of therapy is to suppress viral load to the lowest achievable level. In the patient on zidovudine/lamivudine in whom the HIV RNA rises, it would be reasonable to switch to another two nucleoside regimen (eg, didanosine/stavudine), and to check the viral load four weeks later to determine if adequate suppression of the plasma viral load has been achieved. If adequate suppression is achieved, there are no data to indicate that anything would be lost by delaying the use of the protease inhibitor. If adequate viral load suppression is not achieved, a protease inhibitor could then be added to the two nucleosides.

Dr Hammer: For a patient on zidovudine/lamivudine in whom the plasma HIV RNA level is rising, a number of options exist. If the patient is asymptomatic with only a moderate rise in plasma HIV RNA level (eg, to 15,000 to 20,000 copies/mL), it is certainly reasonable to switch to 2 new nucleosides or to 2 new nucleosides with an NNRTI. In this situation, there would be little lost from deferring the use of the protease inhibitor, based on our current level of understanding. Alternatively, for a patient on zidovudine/lamivudine who is developing HIV-related symptoms, a rapid fall in CD4+ cell count, and a marked rise in plasma HIV RNA level, changing to a more aggressive regimen should be strongly considered. In this case, an alteration in one or both nucleosides along with the addition of a protease inhibitor would be one approach.

51. Many of my patients are on zidovudine/lamivudine. If this regimen fails and knowing that zidovudine/lamivudine/indinavir seems to be good therapy (ie, lowers viral load) would it be reasonable to simply add indinavir?

Dr Hammer: If a patient fails on zidovudine/lamivudine, the simple addition of indinavir is one approach; however, this may not be as efficacious as trying to introduce 1 or 2 new nucleosides along with the protease inhibitor. For example, one can convert a patient on zidovudine/lamivudine to stavudine/lamivudine/indinavir (or ritonavir) or stavudine/didanosine/indinavir (or ritonavir). Another option may be stavudine plus a 2-protease inhibitor combination, such as saquinavir/ritonavir.

Dr Vella: Theoretically, it would be desirable when adding a protease inhibitor to current double RT inhibitor therapy to also change the RT inhibitor(s). However, it may be sufficient to just add a protease inhibitor, if there is evidence that the current therapy is still controlling HIV replication (eg, patients with low viral load).

Dr Montaner: As a rule, if I change regimens, whenever possible I would favor the use of drugs to which the patient has not been previously exposed.

52. Many patients on zidovudine/lamivudine combination therapy have a viral load of around 5000 to 7500 plasma HIV RNA copies/mL. What do we do? Add a single drug (indinavir)? Switch several drugs simultaneously? Which combination would be best? If he/she is reluctant to change therapy, would you consider adding both indinavir and stavudine to this regimen? If four drugs are tolerated and available, should they be tried?

Dr Hammer: If a patient is on zidovudine/lamivudine and is clinically stable with a plasma HIV RNA level of 5000 to 7500 copies/mL, whether to alter therapy depends on a number of factors including the patient's stage of disease, recent CD4+ count trajectory, and available options. Although this level of plasma HIV RNA is perhaps not as low as one would desire or is achievable only in some circumstances, it is still in a category associated with a relatively low rate of progression. If one chose to try to lower the plasma HIV RNA level, the addition of indinavir can be considered if the plasma HIV RNA level and CD4+ cell count have been stable for some time. If, however, it was thought that there has been loss of containment and that the plasma HIV RNA level of 5000 to 7500 copies/mL represented a definitive (>0.5 log) rise from a previous determination, then a change to at least 2 new drugs would be advisable. We do not currently know what the single best alternative regimen would be, but one can change to 2 new nucleosides or change one or both of the nucleosides and move to either a protease inhibitor or an NNRTI. For example, one can change zidovudine/lamivudine to stavudine/didanosine, stavudine/lamivudine/protease inhibitor, stavudine/didanosine/protease inhibitor, stavudine/didanosine/NNRTI or perhaps stavudine with a 2-protease inhibitor combination, such as saquinavir/ritonavir. With respect to the question concerning 4-drug regimens, in general the impact on quality of life, cost, and toxicity profile would make this less desirable for the situation described.

53. Which protease inhibitor should be added to an existing zidovudine/zalcitabine combination, or should a protease inhibitor be substituted?

(Question 53, continued)
Dr Hammer: For patients currently on zidovudine/zalcitabine, any of the currently approved protease inhibitors can be added to this regimen. However, if one were considering the addition of a protease inhibitor to this regimen because of imminent or perceived treatment failure, then it may be best to change the zalcitabine to an alternative nucleoside (eg, lamivudine) at the same time that the protease inhibitor is added or to change both components of the nucleoside regimen (eg, change zidovudine/zalcitabine to stavudine/lamivudine) at the time that the protease inhibitor is added.

54. Should one switch all patients from saquinavir to indinavir or RTIs in view of the potency issue?

Dr Hammer: One should not make the blanket statement that all patients currently receiving saquinavir should be switched to indinavir or reverse transcriptase inhibitors because of the concern about the in vivo potency of saquinavir (related to the low bioavailability of the current formulation). Patients currently receiving saquinavir should be evaluated in the same fashion as any other patient on an antiretroviral regimen—that is by clinical, immunologic (ie, CD4+ cell) and virologic (ie, plasma HIV RNA) status. There are many patients currently doing well on saquinavir-containing combination regimens. Given our still limited antiretroviral options, it would be best to maximize the duration of any currently effective treatment. Further, the issue of the extent of cross resistance of isolates with the saquinavir-associated L90M mutation to other protease inhibitors is still a matter of some debate and it is likely that other protease inhibitor options will remain post-saquinavir therapy.

Dr Vella: The response to this answer in individual patients may depend on the level of HIV inhibition currently achieved by the patient's therapy and on the clinical situation. If a patient is responding to RT inhibitors with saquinavir and the CD4+ count is still greater than 350 cells/μL, it may be useful to continue the patient on while checking carefully for any plasma HIV RNA rebound and keep new RT inhibitors with indinavir or ritonavir as a later option.

55. I understand a single new drug should not be added to a failing regimen. However, why not add lamivudine to zidovudine therapy? Won't this "reverse" zidovudine resistance and thus renew the efficacy of the two-drug regimen?

Dr Yeni: In the case of a zidovudine-resistant virus, adding lamivudine to zidovudine inconstantly reverts the virus phenotype to sensitivity. However, the CAESAR study has demonstrated that adding lamivudine to preexisting zidovudine therapy provides a clinical benefit. Therefore, adding lamivudine to zidovudine, with or without a protease inhibitor, is a possible option, as stated in the *Guidelines*.

Dr Richman: Both the European and North American studies showed that adding lamivudine can reverse zidovudine resistance with temporary benefit. These and other studies have shown more recently that dual resistance with loss of activity of both drugs can also develop. The results of the Merck 035 study (zidovudine/lamivudine/indinavir) suggest that the benefit of this combination results, to a significant extent, from the activity of lamivudine plus indinavir to completely suppress viral replication and to prevent the emergence of lamivudine resistance (the M184V mutation), which in combination with only zidovudine selects for lamivudine resistance within 1 to 2 weeks. This observation raises the question of whether lamivudine should be reserved for combination regimens designed to completely suppress viral replication.

56. If a patient is failing on zidovudine, why keep adding to it?

Dr Yeni: Several clinical trials (Delta, ACTG 175, CAESAR) have documented a clinical benefit in adding a second nucleoside (essentially didanosine or lamivudine) in patients treated with zidovudine. This does not mean that it is the best therapeutic option for every patient. In the case of patients with advanced HIV disease, switching to a new 2- or 3-drug combination may be preferable.

Dr Richman: There are at least two rationales (both unproven) to continue zidovudine in the failing patient. One is that it is well-documented that mixtures of virus, sensitive and resistant, exist in the patient. Zidovudine might assist in dealing with the sensitive population. Second, resistance develops differentially, usually more slowly, in the central nervous system (CNS). Zidovudine that enters the CSF relatively well could still provide benefit in the brain. In addition, it has been documented that lamivudine can "reverse" zidovudine resistance and adds activity to zidovudine in zidovudine-experienced patients.

57. If a patient fails on triple drug therapy, is there a way to assess which drugs are best to replace? Does the virus become resistant in equal amounts to all three?

Dr Yeni: This question underscores the fact that, although significantly expanding, the stock of available drugs is still limited. Therefore, a careful evaluation is required before deciding when and how to change therapy. Viral resistance is the most convincing mechanism to explain a treat-

ment failure defined as an increase in plasma HIV RNA levels. However, viral resistance is not currently assessed in clinical practice and, since time to resistance is known to be different from drug to drug, it is difficult to ascribe treatment failure to a given drug in a combination regimen. In the case of viral load returning to the pretreatment value (or higher) after an initial drop, a complete change of treatment may be justified, because the virus is probably resistant to all drugs in the 3-drug regimen. In the case of a viral load still significantly below the pretreatment value, the decision may be individualized and based on several factors, such as the number of drugs still available to the patient and the plasma HIV RNA level (a more complete change may be indicated in patients with a high viral load).

58. Please comment on raising the doses of one or two of the antiretrovirals in an existing regimen and its effect on viral load and CD4+ before changing regimens?

Dr Hammer: This question is a bit difficult to answer because in general the strategy should be to maintain the maximally potent, safe, and tolerable antiretroviral regimen as much as possible. If this is the strategy that one pursues, then dose increases would only occur after there had been a previous dose reduction for intolerance or toxicity. In those circumstances, re-escalation of the dose of one or more components of a regimen should be attempted when it is deemed safe. However, no general comment can be made about the efficacy of such dose escalations on CD4+ cell or plasma HIV RNA responses because this would depend on many factors, including the length of time the patient had been on the particular regimen, the presence of resistance, and stage of disease, among others. In the case of protease inhibitors, dose escalation may not result in the same plasma HIV RNA response that full doses given up-front would, because resistance may be potentiated by the former approach.

59. Are there strategies to "re-establish" sensitivity to a particular drug? (ie, does lamivudine increase "fidelity of replication"?)

Dr Hammer: Currently, the most clinically applicable strategy to re-establish susceptibility of a virus strain in vivo is to add lamivudine in a zidovudine-experienced patient. In this circumstance, the insertion of the lamivudine-associated codon 184 mutation can re-establish zidovudine susceptibility in isolates that possess the zidovudine-associated resistance mutations. This is probably one of the mechanisms of efficacy of the zidovudine/lamivudine combination in zidovudine-experienced subjects. However, high-level resistance to both agents can emerge. The increased reverse transcriptase fidelity that may be conferred by the lamivudine-associated 184 mutation may limit to some extent the potential for the emergence of genotypic resistance. Whether this is operative in vivo is conjecture at this time.

60. Many patients on stavudine/lamivudine, who have been on a number of NRTIs and have CD4+ counts of about 300 cells/μL and plasma HIV RNA levels of 10,000 to 15,000. Would you recommend a protease inhibitor for these patients? Also, which NRTIs would you recommend?

Dr Schooley: Yes. I would recommend a protease inhibitor-containing regimen in this situation. The nucleoside choices would depend on the prior nucleoside drug history and tolerance of drugs chosen.

61. What is the preferred option for a patient already treated with zidovudine/zalcitabine, changed to zidovudine/didanosine, and changed to zidovudine/lamivudine because of disease progression? Now indinavir added and viral load no longer detectable. Should zidovudine/lamivudine be changed?

Dr Schooley: Continuing zidovudine/lamivudine/indinavir would be reasonable if the plasma HIV RNA level becomes undetectable after such a change.

62. What do you do after switching from zidovudine/lamivudine to two other NRTIs, and viewing a new failure?

Dr Schooley: This is, unfortunately, a problem for many current patients who have been treated with successive nucleosides. In this setting, it might be reasonable to try a combination of ritonavir/saquinavir, monitoring toxic effects and plasma HIV RNA levels closely.

63. What approach should be taken for patients who have tried all currently approved antiretroviral drugs and who demonstrated a "brief" improvement while on two NRTIs and indinavir, but have since shown increased viral loads on testing?

Dr Schooley: In this setting, it might be reasonable to try a combination of ritonavir/saquinavir, monitoring toxic effects and plasma HIV RNA levels closely. If such a plan is contemplated, it would be best to initiate it before high-level resistance to indinavir emerges.

64. For patients who have been on all NRTIs previously and now failing therapy with saquinavir, can we return to a previous NRTI without doing resistance studies? Can indinavir or ritonavir be substituted for saquinavir alone?

Dr Schooley: In vitro testing of viral isolates for susceptibility to antiretroviral drugs is still labor intensive and slow. In the absence of the wide availability of such testing, the use of plasma HIV RNA quantitation after several weeks of a new regimen may be viewed as an "in vivo" susceptibility test. Indinavir or ritonavir can be used alone, but it is quite possible that residual antiretroviral activity may still be provided by nucleosides in this setting, since the definition of "been on" in the question has not been specified. Viral load testing may help sort this out.

65. If you have a patient who has apparent failure to all nucleoside RTIs, would you recommend didanosine and hydroxyurea?

Dr Schooley: The data on this combination are still in evolution. Nonetheless, it would be reasonable to attempt this combination in specific settings depending on the bone marrow reserve and the change in plasma HIV RNA levels. Such patients may also benefit from a trial of combination ritonavir/saquinavir.

66. Many late-stage patients have taken all available drugs as they have become available. Is it wise to first add a protease inhibitor in these late-stage patients?

Dr Schooley: Such patients may benefit from a trial of combined ritonavir/saquinavir.

Dr Hammer: Therapeutic options in patients with advanced disease and extensive antiretroviral experience are naturally limited. This is of particular concern with respect to protease inhibitors. Ideally, one would prefer to add a protease inhibitor in combination with one or two nucleoside analogue reverse transcriptase inhibitors to which the patient had not been previously exposed. However, in circumstances where this is not possible, the simple addition of a protease inhibitor to an existing regimen or to do this with the "recycling" of previously administered nucleoside analogues may be the only options.

67. If patients are failing triple combination therapy (including a protease inhibitor), why haven't we seen the supportive data?

Dr Volberding: Patients have certainly failed "triple therapy." Even in the presented clinical trial data, the benefits were not uniform. In daily practice, failure is seen in compliant patients as well as in noncompliant patients. Also, toxicities and intolerance have resulted in treatment discontinuation, particularly, but not exclusively, in those taking ritonavir.

68. In your opinion, what would be the best time to use the combination of saquinavir/lamivudine, if there is one?

Dr Richman: Given the availability of other more potent protease inhibitors, the role of the current formulation of saquinavir is unclear.

69. If failure of monotherapy is thought to be due to resistance, isn't addition of only 1 new drug functionally the same as monotherapy?

Dr Katzenstein: Yes, although sometimes the addition of one new drug and the continuation of the "old" drug may result in new pressures on the virus. Interactions between the resistance mutations in the *pol* gene, with the addition of one new drug when resistance has developed suggest that adding one new drug may not be the same as monotherapy. For example, a recent study of the addition of lamivudine to ongoing zidovudine therapy suggests that the combination has activity greater than either monotherapy, even in patients who have long-term zidovudine experience and would be expected to have high-level zidovudine resistance. The explanation for this may be that the codon 184 mutation, rapidly selected by lamivudine, resensitizes viruses that contain the codon 215, zidovudine resistance mutation. Nevertheless, dual resistance does develop. In some patients similar interactions have been observed between zidovudine and didanosine, where the addition of didanosine to an existing regimen of zidovudine appears to result in the suppression or prevention of didanosine mutations that arise rapidly when didanosine monotherapy is used.

70. Is there any role for returning to a previously omitted drug or regimen?

Dr Hirsch: Under the best of circumstances, it would be preferable to use drugs to which the patient has not been exposed. However, there may be circumstances in which it is reasonable to recycle previous drugs, particularly in combination with newer agents. For example, if a patient had previously received zidovudine monotherapy and then other agents, it would be reasonable to include a regimen of zidovudine/lamivudine with or without a protease inhibitor in the current therapy.

Dr Yeni: The evolution of viral resistance to a specific drug after the drug has been withdrawn is not well known and is probably different from one drug to another. Because the number of available antiretroviral drugs is not infinite, it may be tempting to return to a drug given years before. Several observations can be made:

1. Since viral resistance is not assessed in clinical practice, no general recommendation can be given for this strategy;
2. The recycled drug should always be combined with a new drug; and
3. This concept may best apply to a zidovudine/lamivudine combination for patients treated previously with zidovudine, given the possible positive zidovudine/lamivudine interaction on viral resistance to zidovudine.

71. With regard to needing to change from zidovudine/lamivudine, how do you take into account CNS penetration when making the change in therapy?

Dr Fischl: CNS complications should be considered when changing therapy, particularly for patients with advanced disease and at least one of the drugs in any regimen should cross the blood-brain barrier.

72. Improvement of AIDS dementia complex (ADC) is well described with zidovudine. Has this been seen with didanosine?

Dr Hirsch: The effects of didanosine on CNS HIV infection have been best evaluated in children in whom beneficial, albeit variable, results have been observed. The variability may result from differing degrees of didanosine absorption among individuals with resultant variable serum and CNS concentrations.

In adults receiving either zidovudine or didanosine orally, CSF concentrations of didanosine are lower than those of zidovudine. Thus, although anecdotal reports of improvement of ADC on didanosine have emerged, data are less convincing than for zidovudine in this setting.

Dr Montaner: I am not aware of any objective data suggesting that didanosine can improve ADC. However, it has often been speculated that we must retain zidovudine as part of our combination therapy regimen to maximize CNS protection. We have recently looked at this issue within a metaanalysis of the controlled trials comparing zidovudine with didanosine monotherapy in zidovudine pre-treated patients. Our results confirmed that a change to didanosine was associated with an improved clinical outcome and surrogate marker response. Also, we found that a change to didanosine was not associated with an increased frequency of CNS problems, specifically ADC. In short, as long as we are effectively treating HIV infection as proposed in the *Guidelines*, I don't think that we need to retain zidovudine in our regimen for fear that we will otherwise see a higher frequency of ADC.

What to Change to: Role of NNRTIs

73. If a patient has used all the nucleosides or cannot tolerate any of the nucleosides, would you add an NNRTI when switching to a protease inhibitor for the first time?

Dr Hammer: If a patient has used all of the nucleosides and there is an indication to change treatment, one can consider adding a protease inhibitor with "recycling" of a previously used nucleoside. In the near future, it may be feasible and appropriate to combine the addition of a protease inhibitor in this circumstance with an NNRTI. Studies are already under way or are planned to look at the pharmacokinetic interactions and activity of NNRTIs such as nevirapine, delavirdine, and DMP-266 with protease inhibitors. Physicians and patients should wait for these studies to be completed before using these combinations, since both classes of drugs are metabolized by the CYP3A4 isozyme pathway. For example, DMP-266 lowers indinavir levels and consequently the proper dose of indinavir to be used in combination with DMP-266 will likely be higher than the currently approved dose. The same may hold true for the combination nevirapine/indinavir. Also, it should be recognized that new nucleosides are on the horizon, such as 1592U89, that may provide future options.

Dr Montaner: A large number of patients today present to us having demonstrated failure or intolerance when treated with multiple nucleosides, alone and in combination. Under these circumstances, our options are seriously compromised. We are not currently in a position to endorse the use of NNRTIs and protease inhibitors in combination. There are possible drug-drug interactions that could advise against these approaches. Clinical trials are under way further exploring these combinations.

What to Change to: Intolerance

74. For the patient on multiple drugs who has side effects requiring a change, how do you sort out which drug is to blame while minimizing monotherapy periods that may induce development of resistance?

Dr Hammer: This is a difficult question for which there is no simple answer. One is often forced to make judgments based on the known drug toxicity profile of a particular

agent and to proceed accordingly. If dealing with a two drug regimen, it may be possible to dose reduce one of the two components rather than stop one of the drugs completely, thereby avoiding a period of monotherapy. However, this may not always be possible. In subjects on triple drug regimens, one may make an educated guess about the most likely offender and dose reduce or stop that drug temporarily while maintaining the other two drugs. This may not always work, however, and if a regimen must be reduced to a monotherapy to sort out potential drug side effects, the period of time should be minimized (ie, on the order of 1 to 2 weeks). Difficulty, however, in maintaining appropriate doses of a particular combination regimen may be a strong indication to change the treatment.

75. If adherence is the key issue, what do you change to if a combination of drugs is started and is then poorly tolerated?

Dr Yeni: Adherence is one of the key issues, but there is not a single response to the question of what to change in a poorly tolerated combination. One should first ask whether intolerance is not related to other drugs, given concurrently, with the antiretroviral treatment. Two methods can be used to identify the drug in the combination responsible for the symptoms of intolerance. One is to sequentially withdraw each drug in the combination, and evaluate the consequences on clinical symptoms. The other one is to withdraw all drugs simultaneously before reintroducing them sequentially following the resolution of clinical symptoms. Several factors may guide the choice of the method in individual patients. One is the probability of correctly ascribing intolerance to a specific drug (eg, mouth ulcers to zalcitabine), allowing for a specific withdrawal. Another factor is the risk of viral resistance if treatment is reduced to monotherapy, even for a short period of time (eg, lamivudine and protease inhibitors), suggesting a simultaneous withdrawal.

Dr Hammer: If a combination regimen is started and then poorly tolerated, it is often a challenge to determine which component of the regimen is responsible. Most often, this is approached somewhat by trial and error, taking into account the known toxicity profiles of the individual drugs. Depending on the nature of the toxicity, one can dose-reduce that component of the regimen that is most likely responsible, but it is not uncommon to have to temporarily stop one or another component of the regimen to reverse the adverse effect and to sort out which drug(s) is (are) responsible. These periods of dose interruption should be minimized, and it is worth reiterating that in the case of protease inhibitors, dose reductions should be avoided, and, if necessary, dose interruptions with restarting of full-dose protease inhibitor therapy is a preferred approach to try to avoid protease inhibitor resistance. If a change is indicated based on intolerance, then, if the options exist, changing within a particular drug class is a reasonable strategy. For example, a patient on zidovudine/lamivudine/indinavir who develops a zidovudine-related toxic effect could have stavudine substituted for zidovudine. Alternatively, a patient on zidovudine/lamivudine/ritonavir who develops intractable gastrointestinal toxic effects related to ritonavir could have indinavir substituted for ritonavir. In the case of changing on the basis of intolerance but when the patient is doing well clinically, immunologically, and virologically, altering only a single component of the regimen is reasonable as opposed to what one would try to do in the case of treatment failure.

76. What combinations do you recommend for patients intolerant to zidovudine and who have marked peripheral neuropathy?

Dr Yeni: In patients with marked peripheral neuropathy, stavudine, zalcitabine, and didanosine should not be prescribed. In the case of intolerance to zidovudine, reintroduction following temporary withdrawal may prove successful. In that case, zidovudine/lamivudine with or without a protease inhibitor can be tried. NNRTIs may also be considered in a combination regimen.

Dr Hammer: For patients with marked peripheral neuropathy, the nucleoside analogue options are obviously limited. In individuals who are zidovudine-intolerant, the approach here depends on the particular intolerance. For example, if it is hematologic intolerance (anemia or neutropenia), the ability to maintain zidovudine as part of the regimen can be enhanced by using hematopoietic growth factors, and, in this situation, it may be worth the inconvenience and expense of using erythropoietin and/or G-CSF. In this way, a double regimen of zidovudine/lamivudine or triple regimens including zidovudine/lamivudine and either a protease inhibitor or an NNRTI could be maintained. If, however, there is a zidovudine-related toxic effect that cannot be overcome, then one may be left with a 2-drug combination of lamivudine/protease inhibitor or lamivudine/NNRTI. As pharmacokinetic interaction data emerge, using lamivudine with 2 protease inhibitors (eg, saquinavir and ritonavir) or ultimately lamivudine with a protease inhibitor and an NNRTI would be additional options. However, protease inhibitors should not be used with NNRTIs until the pharmacokinetic interaction data are available. An additional future nucleoside analogue option for patients who develop zidovudine intolerance in the setting of marked peripheral neuropathy may be the investigational nucleoside 1592U89.

Dr Montaner: This represents a difficult challenge in clinical practice. Recently, data have been presented regarding the combined use of saquinavir and ritonavir. Ritonavir substantially decreases the metabolism of saquinavir and therefore it enhances its antiretroviral effect. The combina-

Improving the Management of HIV Disease:

HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management

The International AIDS Society-USA (IAS-USA) is pleased to present its calendar of continuing medical education programs for the winter/spring of 1997. The IAS-USA offers state-of-the-art programs as part of a nationwide continuing medical education effort for physicians on the ever-evolving challenges of HIV disease. The programs listed below provide current information/new findings on HIV pathogenesis; viral load monitoring in clinical practice; recent clinical trial results of new antiretrovirals and combination strategies for the optimal use of antiretroviral drugs; compliance/adherence; and prevention and treatment of opportunistic complications, including CMV, MAC disease, and others. Precise topics and faculty differ for each regional conference.

Registration fees to the full-day course include attendance, CME credits (6 to 7 hours per course), course materials, and lunch. Registration is open to physicians involved in HIV/AIDS care; other health care professionals are welcome. Registration is limited, and courses may fill early. Therefore, we encourage early preregistration.

This calendar provides preliminary program information regarding dates, location, and fees. You may use the form provided to request additional information. Complete program brochures are usually available 8 to 12 weeks before the program. For further information or assistance, please call the IAS-USA at (415) 675-7430. We may also be reached by fax at (415) 675-7438 or e-mail at IASUSA1@aol.com

The 1997 Winter/Spring Symposia Schedule

Course locations and dates	Early registration fee	Course number
Atlanta, Georgia, **Thursday, February 13, 1997** Chair: Michael S. Saag, MD, Co-chair: Melanie A. Thompson, MD	$25.00	7-250
Los Angeles, California, **Saturday, February 22, 1997** Chair: Ronald T. Mitsuyasu, MD, Co-chair: Paul A. Volberding, MD	$25.00	7-210
New York, New York, **Friday, March 7, 1997** Chair: Gerald H. Friedland, MD, Co-chair: Paul A. Volberding, MD	$35.00	7-220
San Francisco, California, **Tuesday, April 15, 1997** Chair: Paul A. Volberding, MD, Co-chair: Stephen E. Follansbee, MD	$25.00	7-240
Chicago, Illinois, **Wednesday, April 30, 1997** Chair: John P. Phair, MD, Co-chair: Harold A. Kessler, MD	$25.00	7-200
Cleveland, Ohio, **Saturday, May 17, 1997** Chair: Michael M. Lederman, MD, Co-chair: Michael S. Saag, MD	$25.00	7-280

International AIDS Society-USA General Information

Organization

Established in 1992, the International AIDS Society-USA is a national not-for-profit education organization exempt from tax under section 501(c)(3) of the Internal Revenue Code. Our mission is to provide fair-balanced, scientifically rigorous, clinically relevant, and timely medical education to physicians who provide medical care for people with HIV/AIDS. The advanced-level CME programs aim to bridge clinical research with patient care.

Audience

The International AIDS Society-USA CME programs are designed as advanced courses for physicians who actively care for people with HIV/AIDS. In planning the programs, we assume that the audience is knowledgeable about HIV disease, which allows us to focus on high-level, cutting-edge information. The courses are designed for physicians, but all clinicians are welcome.

Programs

1997 will mark the fifth year of our national CME effort focusing on viral pathogenesis of HIV disease, antiretroviral therapy, and issues in selected populations with HIV. The program consists of full-day symposia in cities across the United States, and aims to integrate basic science with clinically relevant information.

Please return this completed form with the appropriate box checked.

Note: Program titles, registration fees, credit hours, dates, and locations are subject to change. Please contact the IAS-USA office to confirm the program details and to receive a complete course brochure.

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Please send information on the following (check all that apply)

- ☐ Atlanta, Georgia, Thursday, February 13, 1997
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- ☐ Chicago, Illinois, Wednesday, April 30, 1997
- ☐ Cleveland, Ohio, Saturday, May 17, 1997

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tion is reasonably well tolerated and it provides viral load decreases of approximately 2 logs for 12 to 24 weeks. Saquinavir/ritonavir with or without lamivudine would therefore represent a reasonable option for those patients intolerant to zidovudine who have severe peripheral neuropathy.

77. How would you treat a patient with severe peripheral neuropathy who has had zidovudine and lamivudine for over a year, with a falling CD4+ count?

Dr Yeni: If the fall in the CD4+ count is not associated with intercurrent infection and is related to treatment failure, a change in treatment is required. A protease inhibitor is a good option, but, in this case, it is difficult to select the drug to combine it with because of severe neuropathy (stavudine, zalcitabine, and didanosine should not be used) and zidovudine/lamivudine failure. Two options should be considered. One is to add a protease inhibitor to zidovudine/lamivudine, but the effect of treatment may be short-lived if viral load is high. Another option is to switch to a combination of a protease inhibitor and an NNRTI, but the drug/drug pharmacokinetic interactions as well as the tolerance to such a combination are unknown and require very careful monitoring for toxic effects. Until more information is available, I would select the first option.

78. What can the Panel recommend about "dose modifications" for 3 drug combinations that include protease inhibitors, in case of intolerance due to interactions with drugs used for OIs?

Dr Hammer: With respect to dose modifications in individuals on protease inhibitors as part of triple-drug combinations, our current level of understanding would suggest that a dose reduction of the protease inhibitor component should only be done if no other option exists. Given that it may represent the most potent component of a triple drug regimen, it would be preferable to modify the doses of the nucleoside drug and try to maintain full doses of the protease inhibitor if possible. However, this is not always possible, and if necessary, the dose reduction of the protease inhibitor should be minimized. For example, indinavir should be reduced from 800 mg q 8 hourly to 600 mg q 8 hourly rather than proceeding to an immediate 50% reduction when an adverse event mandates a dose adjustment.