At the symposium in Geneva, the approximately 3000 participants were invited to submit questions for the Antiretroviral Therapy and Resistance Testing panels to address. It would have been impossible to answer all the submitted questions, but we have attempted to address each of the major scenarios/problems presented in the questions submitted. Questions and responses have been grouped into categories reflecting the major issues raised.

Some of the questions raise issues for which there are no scientifically valid answers at this time. The panels have based their responses on basic science and clinical trial data where they are available, as well as on their own interpretations of available data. Thus, the different members of the panel may have different opinions or recommendations. These observations indicate that many of the questions were, quite appropriately, right on the cusp of advancing knowledge in this field, and that there is still a great deal to be learned about the optimum use of the therapeutic agents that are already at hand.

Because of the continued evolution of treatment of HIV disease, the IAS–USA Panels will continue to provide updated recommendations at a pace consistent with the availability of new scientifically valid data. The comments below are the opinions and recommendations of the individual panel members and do not represent a consensus of either of the International AIDS Society–USA panels. Rather, these discussions are meant to provide feedback on some of the complicated issues involved.

1. **ACUTE INFECTION**

1. Is a protease inhibitor-based regimen recommended for every case of primary HIV infection? Should we consider not including protease inhibitors in triple-drug combinations for some patients with primary HIV infection, given the metabolic disturbances that are emerging and the known 5-year coronary risk?

**Dr Montaner:** There is considerable controversy regarding the best approach to the management of HIV infection in antiretroviral therapy–naïve individuals. Triple-drug combination with 2 nRTIs and a potent protease inhibitor was thought to be the standard of therapy at all stages of the disease over the last couple of years. Initially, the results of the INCAS trial evaluating nevirapine and, more recently, confirmatory results from trials evaluating delavirdine and efavirenz have further opened the door for us to consider 2 nRTIs plus an NNRTI as a potential treatment option. Beyond that, early data presented by Margaret Fischl at the Geneva conference highlighted the possibility of using triple nRTI regimens (e.g., zidovudine/lamivudine/abacavir) from early clinical testing with similar results. Similarly, the issue remains controversial in the area of primary HIV infection where unfortunately very little controlled data exist on which to base a recommendation. At this time, therefore, our patients with primary HIV infection who are not willing or able to participate in randomized clinical trials are offered triple-drug therapy using the same principles that apply to initiation of therapy in chronic HIV infection.

2. **Would you recommend a 4-drug regimen that includes hydroxyurea and didanosine for someone who has recently become PCR-positive, is HIV antibody-seronegative, and had symptoms of acute retroviral syndrome?**

**Dr Yeni:** Interesting preliminary results have been obtained in treating a small number of patients with HIV primary infection by a combination regimen including didanosine, hydroxyurea, and
indinavir. In a few cases, HIV proviral DNA was not detected in the lymph node cells of treated patients, and HIV could not be cultured in vitro. However, given the very limited data available and the potential for toxic effects with such a combination, more scientific information is necessary before any recommendation can be safely made about the use of hydroxyurea in primary infection.

**Dr Montaner:** Several groups have now conclusively demonstrated the ability of hydroxyurea to enhance the antiretroviral effect of nRTIs. This has been most thoroughly documented for didanosine, but it is at least possible that the efficacy may extend to most if not all nRTIs. This effect has been demonstrated both in naive- and chronically nRTI-treated patients. A second consistent finding across studies using hydroxyurea relates to the decreased CD4+ cell response that is associated with this treatment. As pointed out by Dr Yeni, interesting results were recently presented in the form of a small case series or case reports where patients treated with hydroxyurea-containing regimens during primary infection did not demonstrate a rebound viral replication after completing several months of highly suppressive therapy.

Given the uncontrolled nature of these observations, one should be extremely careful in drawing any conclusions from these data. At this time the possible role of adjunctive hydroxyurea therapy in primary infection should be regarded as experimental. This is a very important and urgent question that needs to be addressed in a prospective, randomized, controlled trial.

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**3. A 19-year-old woman was HIV-seronegative in 11/97 and HIV-seropositive in 2/98 (she had no acute symptoms). In March 1998, her CD4+ cell count was 640/μL and plasma viral load was 64,000 copies/ml. In April 1998, her CD4+ cell count was 610/μL and plasma viral load was 14,000 copies/ml. Would you recommend initiating therapy at this point for this patient? If so, what regimen would you suggest?**

**Dr Hirsch:** I would recommend continued virologic and immunologic monitoring, but not immediate initiation of therapy. This individual has been infected for 2 to 5 months, and it is not clear that her plasma virus titer has yet reached its nadir. Once a virologic set-point is reached, she should be reevaluated and further therapeutic options should be considered.

Had she been seen earlier, during acute infection, I would have recommended aggressive antiretroviral treatment, on the possibility that such therapy could reduce the virus set-point, diminish the likelihood of subsequent viral heterogeneity and resistance, and maintain optimal immune responsiveness. However, we are now beyond that acute period, and the risks and benefits of aggressive intervention are less clear.

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**II. INITIAL THERAPY IN ESTABLISHED INFECTION**

**4. Combination didanosine/hydroxyurea is being used in sub-Saharan Africa. Please comment on this approach.**

**Dr Katzenstein:** I think we must recognize that the recommendations of the IAS-USA panel, the US Public Health Service, and others do not take into account the economic and practical issue of antiretroviral therapy in resource-limited countries. Even HIV-seropositive individuals with the means to afford 3- or 4-drug regimens may find it very difficult to access consistent supplies of the different drugs in much of the world. There are demonstrated benefits to didanosine monotherapy. Didanosine can be used as a single daily dose of 400 mg and, although resistance to didanosine will eventually develop, prolonged didanosine therapy does not result in high-level cross-resistance to other nRTIs. Hydroxyurea enhances the activity of didanosine, even after genotypic and phenotypic evidence of viral resistance to didanosine are demonstrated. Depending on the urgency of treatment, didanosine may be used alone as initial
therapy. From the didanosine monotherapy arm of ACTG 175 we know that didanosine “buys” on average at least 2 years of increased CD4+ cell count and decreased plasma HIV RNA level in early HIV infection. Data on didanosine and hydroxyurea suggest that increased plasma HIV RNA suppression occurs with the combination, even when hydroxyurea is added after several years of didanosine exposure. The most efficient use of these 2 drugs may be to add hydroxyurea in response to evidence of progression (rising HIV RNA level, falling CD4+ cell count, or development of symptoms). This must be balanced against the risks of neutropenia and bone marrow suppression with long-term hydroxyurea use.

**Dr Montaner:** Current therapeutic guidelines are based on the principle that high-level suppression of viral replication will be associated with decreased morbidity, mortality, and immunologic recovery. The difference between partially and highly suppressive regimens is largely attributable to the ability of the highly suppressive therapies to minimize the chances of viral rebound and therefore emergence of resistance. This is fundamentally responsible for the more profound and durable benefit associated with highly suppressive therapies. On the other hand, there is no doubt that partially suppressive therapeutic strategies have led to improved clinical outcomes as described by Dr Katzenstein above.

I would be extremely hesitant to endorse a policy of using less than highly suppressive therapy (ie, triple-drug therapy) as this could open the door for policymakers to embrace suboptimal therapeutic strategies, which in my opinion should be strongly discouraged.

**Dr Yeni:** Given the continuum of increased risk of progression of HIV disease with increasing baseline plasma HIV RNA level, there is no “magic” threshold plasma HIV RNA value for deciding when to initiate therapy in patients with established HIV infection. The recommended range of 5000 to 10,000 copies/mL is a compromise incorporating some degree of approximation.

In patients tested for plasma HIV RNA in the absence of recent immunization or ongoing infection, the test variability is 0.3 log (twofold), which is low, given the spectrum of observed RNA values. Increasing the number of tests to more than 2, in order to more accurately assess the baseline plasma HIV RNA level, would result in an excessive refinement, given the approximation of the recommended threshold value for therapy. Taking into account other parameters, such as changes in CD4+ cell count and plasma RNA level over time and patient commitment to therapy, is more appropriate at this stage of the decision-making process.

**Dr Saag:** I agree, 2 baseline tests are generally adequate to make treatment decisions in this setting. In a patient with a CD4+ count above 500 cells/μL, most clinicians will not recommend that antiretroviral therapy be initiated until viral load values are confirmed to be at least 5000 to 10,000 copies/mL. It would be unusual for viral load values to fluctuate between 5000 and 30,000 copies/mL, for example. Therefore, 2 baseline tests should confirm whether the viral load is in the range where treatment should be initiated; if the levels are in the “observe” range (below 5000 to 10,000 copies/mL), follow-up HIV RNA values should be obtained about every 3 months.
7. A 46-year-old woman started an initial regimen of zidovudine/zalcitabine/saquinavir. Over the first 30 months on this regimen, CD4+ cell count rises (to approximately 450/µL) and plasma viral load drops to below detectable levels. Now the plasma viral load is >5000 copies/mL. What regimen would you recommend for her at this point?

**Dr Hammer:** The baseline CD4+ cell count and plasma HIV-1 RNA level are not described for this case, but one can infer that there was an excellent response to the initial regimen of zidovudine/zalcitabine/saquinavir. Assuming that virologic failure has been confirmed by more than 1 plasma HIV-1 RNA determination and that possibilities such as nonadherence, intercurrent illness, or vaccination have been excluded, there are a number of potential choices for a new antiretroviral regimen. The basic tenet that all drugs in the regimen should be changed can be adhered to in this case given the options available. One option is to change the nRTI regimen to stavudine/lamivudine and to combine this with a dual protease inhibitor regimen such as indinavir/nelfinavir or indinavir/ritonavir, although substantially more clinical trial data will be needed to know if these dual protease inhibitor regimens will prove helpful in a circumstance such as this. A second option would be to combine stavudine/lamivudine with a protease inhibitor such as indinavir or nelfinavir and an NNRTI such as efavirenz. It should also be noted that some patients in whom saquinavir is failing will respond to the dual protease inhibitor regimen of ritonavir/saquinavir, the dual protease inhibitor for which there is the greatest clinical trial experience. However, as we gain experience with other dual protease inhibitor regimens, it is perhaps best to try to change all the drugs if possible. There is no guarantee of success with any regimen, of course, because of the potential for drug cross-resistance, toxicities that limit adherence, etc. Lastly, if the tests are available, a decision would need to be made as to whether phenotypic or genotypic resistance testing might assist with the choice of the alternative regimen.

**Dr Vella:** The patient started antiretroviral therapy with a regimen that was clearly effective but whose potency was not maximal. At this point, with plasma viral load back to detectable levels, it is probable that some degree of viral resistance has emerged and a change in the regimen is desirable. I agree that the patient might switch to an entirely new 3-drug combination, including a new protease inhibitor (eg, stavudine/lamivudine/nelfinavir). As an alternative, a regimen including an NNRTI instead of a protease inhibitor might be considered, although only scattered data are available regarding switching from protease inhibitor-containing regimens to those including an NNRTI.

**Dr Fischl:** Zidovudine monotherapy has been shown to be inferior to combination regimens related to initial immunologic, virologic, and clinical responses. Similar data have been noted with monotherapy with other nRTIs such as zalcitabine and lamivudine, with NNRTIs, and with HIV-1 protease inhibitors, when evaluating immunologic and virologic responses, and in some settings, clinical responses. Although initial increases in CD4+ cell counts and decreases in HIV RNA levels may be seen, monotherapy regimens result in the emergence of viral resistance and thus subsequent loss of benefits. With the use of monotherapy NNRTI and protease inhibitor regimens, broader class resistance is likely.

Zidovudine, as with other nRTIs, has been a cornerstone drug when building potent triple-drug regimens for the treatment of HIV infection that include either all nRTIs (eg, zidovudine, lamivudine, and abacavir), NNRTIs (eg, zidovudine, lamivudine, and either nevirapine or efavirenz) and HIV-1 protease inhibitors (eg, zidovudine, lamivudine, and either indinavir, nelfinavir, or saquinavir-soft gel capsules, or dual protease inhibitor-containing regimens such as ritonavir/saquinavir).

8. Why is zidovudine still included in the different recommended antiretroviral regimens? Don’t we know from results of the past 10 years that there was no benefit using zidovudine?
9. A 34-year-old man was diagnosed approximately 3 years ago with CD4+ count 1000 cells/μL and plasma viral load 10,000 copies/mL. He now has a CD4+ count of 900 cells/μL and viral load of 30,000 copies/mL (by repeated testing 3 months apart); he remains asymptomatic and has not started antiretroviral therapy. In light of the laboratory variability of CD4+ cell counts, do you think the 100 cell/μL decline in CD4+ count is due to the HIV infection or simply explained by laboratory variability? Would you recommend therapy for this patient?

**DR SAAG:** While CD4+ counts at this level (about 1000 cells/μL) may vary as much as 100 cells/μL between timepoints due to biologic variability, I think the decrease in this case is most likely due to the virus. In the Multicenter AIDS Cohort Study (MACS), patients with viral load levels below 5000 to 10,000 copies/mL had an average CD4+ cell loss of 40/μL per year. Therefore, a decline of 100 cells/μL over a period of 3 years would be expected in a patient with a viral load of about 10,000 copies/mL. The decision to treat or not is driven in this case more by the current viral load value, which has risen to 30,000 copies/mL. If the patient is willing to start therapy and commit to taking medications routinely, I favor initiation of therapy at this time. I would tend to recommend a protease inhibitor–sparing regimen (e.g., 2 nRTIs plus an NNRTI or a triple nRTI regimen) that could be taken once or twice daily. If the patient is not committed to starting therapy at this point, I would continue monitoring, including viral load testing every 2 to 3 months and CD4+ counts every 4 to 6 months.

10. Do you consider phenotyping for all initially diagnosed patients in areas such as Newark, New Jersey, where there are high incidences of infection–drug–related and heterosexual transmission, and a lot of patients who are on therapy but not adherent to the antiretroviral regimens?

**DR LOVEDAY:** In our center in the United Kingdom we have now decided to screen all drug-naive patients to determine the individual and community prevalence of viral resistance. This serves two functions: first, to monitor the problem of resistance locally and its rate of evolution, and second, to ensure that no new patient now starts triple therapy with drugs to which they may carry pre-existing resistance-conferring viral mutations.

The question specifically addresses the use of phenotypic resistance in this exercise. We have been impressed by the data from our own collaborative trials and others that show the good correlation between phenotypic and genotypic results, and as such we have elected to use genotyping from plasma HIV RNA, derived from viral load quantification, by automated sequencing to detect mutations that are known to be associated with viral resistance. This is providing very extensive data that will also contribute to scientific research. Nonadherence to therapy is a separate issue and must be urgently addressed.

11. In an asymptomatic patient who has more than 500 CD4+ cells/μL and about 10,000 copies/mL of plasma HIV RNA, the risk of progression is 10% in 3 years. If a protease inhibitor is started, the risk of lipodystrophy is much higher (50% in 1 year?). Does the risk of lipodystrophy outweigh the potential benefits of therapy?

**DR YENI:** There is, at present, no definitive answer to this important question. More data are needed about the epidemiology of lipodystrophy in treated HIV-infected patients, as well as about other complications of therapy such as increased levels of plasma triglycerides or cholesterol levels. If a 10% risk of progression of HIV disease in 3 years is acceptable, such a risk is cumulative with time and the level of individual acceptance is variable. An appropriate solution would be to treat this patient at an early stage of HIV disease with a potent protease inhibitor–sparing regimen. Unfortunately, there is less information available on the long-term activity and toxicity of protease inhibitor–sparing than of protease inhibitor–containing regimens. Clearly, the decision to initiate therapy and the choice of treatment are difficult in such patients, and should be individualized; an in-depth discussion with the patient, including a thorough explanation of the benefits, risks, and uncertainties of each strategy, is a critical step.

**DR HIRSCH:** As Dr Yeni noted, the true incidence of clinically significant lipodystrophy is unclear, as is its etiology and
pathogenesis. Prospective controlled trials, such as ACTG 384, are attempting to clarify the true incidence and whether this problem is related to treatment with protease inhibitors or is related to potent virus suppression by any regimen. It is not clear whether “protease-sparing” regimens will prevent this complication. The risks of therapy and the risks of delay should be discussed with the patient, and an informed decision should be made. In my view, the risks of not treating probably outweigh the risks of significant lipodystrophy.

12. What about the use of the combination didanosine 400 mg once a day/indinavir 1200 mg q 12h/stavudine 40 mg q 12h, as a “comfortable” combination to improve adherence?

Dr Hatzenstein: Most adherence studies indicate that the “midday” dose is the most frequently missed one. Patients often have difficulty, with work and travel schedules, remembering to take the midday doses. Patients are always looking for the most convenient bid dosing schedules. A potential difficulty of the regimen proposed could be the ability to consistently take 400 mg of didanosine (on an empty stomach) followed 30 to 60 minutes later by indinavir (indinavir should be taken on an empty stomach or with a light meal or snack, if needed for better tolerance). There may be only a small advantage to once-daily dosing didanosine while all other drugs in the combination are taken twice or three times daily. I would begin this regimen with careful monitoring of the patient’s tolerance for a large, early-morning dose of didanosine, with plans to either split the didanosine dose, or move the didanosine dose to a midday dose if needed. Of note, current data (October 1998) indicate that bid dosing of indinavir is significantly less effective than tid dosing as a component of potent antiretroviral therapy.

13. In a therapy-naïve, HIV-seropositive patient with CD4+ count of 20 cells/µL, will starting a very aggressive 4-drug or 3-drug therapy cause the subject to have a larger CD4+ pool? Will this thus raise the plasma HIV RNA level?

Dr Hammer: There is the theoretical possibility that the greater CD4+ cell count rise induced by the most potent antiretroviral drug combinations available will increase the target cell population and thus paradoxically raise the plasma HIV-1 RNA level. Such a possibility has been raised as one of the factors involved in the failure of simplified maintenance regimens in the ACTG 343 induction maintenance trial. In that study following successful induction on a regimen of indinavir/zidovudine/lamivudine, one of the predictors of failure in patients randomized to less intense regimens following virologic suppression was an early rise in the CD4+ cell count during induction. This, however, is a much different circumstance than the one described in this case. An individual with a CD4+ cell count of only 20/µL and presumably a substantial plasma HIV-1 RNA level is at high risk of disease progression and is deserving of the most potent treatment. Successfully suppressing virus replication to the greatest degree possible (ie, to <20–50 copies of HIV RNA/mL) will clearly limit the risk that new CD4+ cells will become infected. In fact, the greatest way to protect proliferating CD4+ cell counts is to maximize viral suppression. Further, it should be noted that successful antiretroviral therapy is associated with a diminution in activation markers on the surface of CD4+ cells, thus making them theoretically less able to support virus replication. Finally, ACTG 320 demonstrated that clinical disease progression can be significantly slowed by the use of more potent (ie, a 3-drug regimen including a protease inhibitor) compared with a less potent regimen (ie, a dual NRTI combination). Thus, all the evidence weigh in favor of being aggressive in this case.

14. Is there a preferred antiretroviral regimen for an HIV-seropositive patient with Kaposi's sarcoma?

Dr Volberding: Most patients with Kaposi's sarcoma should be treated with aggressive protease inhibitor–containing drug combinations. Clearly, these patients have a complication of HIV disease and require aggressive antiretroviral therapy. A response of the Kaposi's sarcoma may occur with protease inhibitor–sparing regimens, but much more experience has been gained with the protease inhibitor–containing regimens as elements of the regimen, so I would probably recommend including them until more experience is gained with other approaches. There are no specific combinations of antiretroviral drugs that have demonstrated efficacy for Kaposi's sarcoma, but if aggressive chemotherapy is required, attention must be paid to the possibilities of drug interactions and toxic effects, especially neutropenia and peripheral neuropathies.
III. DOSING/ADMINISTRATION

15. Is there a rationale for not using 2 NNRTIs together?

Dr Hammer: The rationale thus far for not using NNRTIs together has been that they, for the most part, bind to the same region on the reverse transcriptase enzyme and thus would theoretically compete with one another. Further, there is the theoretical concern that combining these drugs clinically might enhance their toxicity profiles, particularly with respect to rash. There are, however, no data to speak to this at this time. This being said, it should be noted that some in vitro studies suggest that NNRTIs can be additive or synergistic when used together and there are some early reports of using 2 NNRTIs together as part of 6-, 7-, and 8-drug regimens in a salvage situation, an approach that has been termed “mega-HAART.” Whether potency is truly enhanced by this approach is uncertain, and the class cross-resistance that is known to be a problem for the NNRTIs may not be circumvented. NNRTIs individually are quite potent and the successful use of these drugs is directly linked to the strength of the rest of the antiretroviral combination employed in order to try to limit virus replication and the emergence of mutants that are resistant to the NNRTIs and other drugs.

Dr Conway: This is clearly an issue that needs to be addressed in clinical research. Potential problems of combination NNRTI therapy would include synergistic toxicity (particularly an increased incidence of rash if delavirdine and nevirapine are used) and some deleterious pharmacokinetic interactions, as efavirenz and nevirapine are net inducers of the hepatic cytochrome system (CYP3A4) and delavirdine is a net inhibitor of this metabolic pathway. It is not known whether a combination of 2 NNRTIs would enhance the potency of a given maximally suppressive antiretroviral therapy regimen. In theory, there could be a benefit in terms of such a combination, as certain isolates that are resistant to delavirdine may retain some degree of susceptibility to efavirenz and may be resensitized to nevirapine (if they had become resistant to this drug), leading to prolonged efficacy of the NNRTI component of a regimen after the first resistance mutations have begun to emerge. If preliminary pharmacokinetic studies support the feasibility of combining NNRTIs while maintaining appropriate therapeutic blood levels, the approach should be evaluated within the context of a well-designed clinical trial.

16. Are there any data about twice-daily dosing of nelfinavir and saquinavir hard gel capsules?

Dr Vella: A twice-daily dosing of nelfinavir is being explored in clinical trials. Preliminary results seem favorable but should be confirmed in larger studies. Twice-daily dosing of saquinavir hard gel formulation is possible only when the drug is used in combination with other drugs (eg, ritonavir) that improve pharmacokinetics.

IV. CHANGING/CONTINUING THERAPY

17. Is it still true that “plasma HIV RNA rebound should be the main trigger for changing therapy” given the genotypic data presented at the Drug Resistance Workshop in Lago Maggiore (June 1998) showing that genotype data can be an “early warning” for the need to change therapy?

Dr D’Aquila: The most current data continue to indicate that plasma HIV RNA rebound should be the main trigger for when to change therapy. Testing for either genotypic or phenotypic evidence of resistance is less likely to yield a result with any of the current methods if plasma HIV RNA is less than about 1000 copies/mL. There were several retrospective studies presented in Geneva and at the recent Drug Resistance Workshop that suggested that resistance testing may help in a different way: to choose which drugs not to use in the next regimen. Each of these studies found that detection of baseline genotypic or phenotypic evidence of resistance to one or more drugs in a salvage regimen was a reliable predictor of failure of that salvage regimen.

Dr Richman: The reemergence of detectable plasma HIV RNA defines therapeutic failure. This is not sufficient, however, to trigger a change in therapy. Before changing, it is important to ascer-
tain whether the patient has been adherent to the regimen, whether there are pharmacologic or gastroenterologic reasons for suboptimal plasma levels of drug, and whether the detectable levels are confirmed on repeat testing. Because options are limited, changes should not be made without compelling reasons. On the other hand, newer data suggest that delayed change may diminish future options. Therefore, concern about impending failure dictates closer monitoring.

to use hydroxyurea plus didanosine and possibly stavudine and/or lamivudine plus ritonavir and saquinavir in addition to an NNRTI.

**19. In the setting of protease inhibitor failure, should a protease inhibitor still be maintained in the regimen in order to hit that target?**

**Dr Saag:** It depends. The likelihood of success of a protease inhibitor working after failure of a previous protease inhibitor is dependent upon the situation and the mechanism of failure. If the first protease inhibitor induced only a few mutations that do not confer cross-resistance to the subsequent protease inhibitor, there is a reasonable chance of success for the new protease inhibitor–containing regimen. Conversely, if multiple mutations that confer cross-resistance exist, the chance of success is much lower. In this setting, dual protease inhibitor therapy, along with 2 other drugs that the patient (ideally) has not taken previously, may be necessary. However, success with this approach is variable. Many clinicians adopt a strategy of changing therapy relatively early when their patients experience a confirmed rebound of viral load (eg, 500 to 5000 copies/mL, confirmed) in order to minimize the emergence of multiple mutations that will confer cross-resistance.

**20. Where do you recommend the use of zalcitabine for retreatment? When phenotypic testing shows that the HIV RNA strain is sensitive to it?**

**Dr Yeni:** The short- and long-term consequences of switching the protease inhibitor for an NNRTI in patients with viral load levels below detectable limits on 2 nRTIs plus a protease inhibitor is currently under investigation. Until more information is available, such a strategy cannot be uniformly recommended. If the patient is concerned about, but not experiencing, protease inhibitor side

**Dr Fischl:** Zalcitabine has been shown to have modest antiretroviral activity when combined with other nRTIs in patients who are antiretroviral treatment–naive. However, several studies have shown that zalcitabine-containing regimens are less potent than other nRTI combinations in patients with prior antiretroviral treatment experience. This has led to limited use of zalcitabine when constructing alternative regimens for patients with prior nRTI experience, regardless of resistance studies.

**18. This patient is currently taking 2 nRTIs and indinavir. He has extensive previous exposure to all antiretrovirals except the NNRTIs. Plasma viral load is 125 copies/mL for the past 2 years on stable therapy. Would you add an NNRTI (eg, efavirenz), add another protease inhibitor, change all drugs in the regimen, or not make any changes?**

**Dr Montaner:** The case described poses an extremely difficult but real clinical situation. There is an increasing number of patients who arrive at the clinic on triple-drug therapy regimens consisting of 2 nucleosides plus a potent protease inhibitor with a low plasma viral load and a history of prior plasma viral load rebound while on all other available agents. In these patients, despite the absence of controlled clinical trial data, we feel that intensification of the treatment is warranted in order to avoid continued evolution of the virus and ultimately high-level resistance to all available drugs. One possible approach would be to stop the current regimen and then...
22. A patient is taking stavudine/didanosine/indinavir. After about 8 months, he developed hyperbilirubinemia, and a rise in his creatinine level was attributed to indinavir. Despite reduction of indinavir to half the dose and finally discontinuing the drug, the patient still has hyperbilirubinemia. He had taken zidovudine, ritonavir, zalcitabine, and lamivudine at different times.

23. In antiretroviral-experienced patients, using hydroxyurea does not result in increases in absolute CD4+ cell numbers. Consequently, given its probable low therapeutic index, will the drugs actually accelerate the development of opportunistic infections?

Dr Montaner: I concur completely with Dr Yeni’s remarks. In the absence of controlled data we would not encourage patients to switch from a 2 nRTI plus a potent protease inhibitor regimen to a 2 nRTI plus an NNRTI regimen unless there is a clear need to do so. In that case, if the patient is highly suppressed with a plasma viral load below 400 copies/mL (and hopefully by now with a plasma viral load consistently below the limit of detection of the more sensitive assays), one should be in a reasonable position to offer a switch from a potent protease inhibitor to an NNRTI without altering the 2 nRTI backbone.

Dr Vella: As a first step, the patient should be evaluated for nonpharmacologic causes of hyperbilirubinemia. If these are ruled out, and if there are no signs of liver dysfunction, the patient may continue to take didanosine, because it is rare that this drug just causes an isolated hyperbilirubinemia.

Tentatively, the patient may switch to a regimen of stavudine/didanosine/nelfinavir. Indeed, if the patient had taken lamivudine in the past and changed the regimen because of virologic failure, it might not be acceptable to reintroduce this drug because resistant virus might already be present.

Dr Kuritzkes: I agree with Dr Vella. There is no apparent reason for the persistent isolated hyperbilirubinemia. A medical workup for this persisting problem is therefore warranted. I agree with changing from indinavir to nelfinavir, but would suggest that the nRTIs be left unchanged. An alternative to nelfinavir would be a change to an NNRTI such as nevirapine or efavirenz.

Dr Hirsch: The clinical benefit of hydroxyurea in HIV infection has not yet been clearly established. When used in combination with certain nRTIs, particularly didanosine, it can potentiate antiviral activity. However, CD4+ cell count responses may be blunted by hydroxyurea. When combined with more potent regimens including protease inhibitors, or when added several weeks after initiation of antiretroviral drugs, this blunted CD4+ cell response may not be seen. There is no evidence that hydroxyurea will accelerate the development of opportunistic infections, but it must be used cautiously in patients with poor bone marrow reserves because of its capacity to cause leukopenia or thrombocytopenia.

Dr D’Aquila: It is important to use hydroxyurea, which does not directly target HIV, only in combination with certain antiretrovirals. There are increasing data showing immunologic as well as virologic benefits of didanosine/hydroxyurea (with or without additional drugs). While the CD4+ cell count increases are modest at best, opportunistic infections have not been reported. In 1 small cohort reported by Lori et al, T-helper cell proliferative responses to HIV antigens were reconstituted in almost half of the patients who took hydroxyurea for more than 2 years. This is the best example reported to date of reconstitution of HIV-specific immune responses with treatment of established infection. It is my personal bias, however, that hydroxyurea may be best used as a component of
24. For a patient with more than 500 CD4+ cells/μL taking a 3-drug regimen that contains a protease inhibitor, which is more worrisome: a plasma viral load of 1000 copies/μL or a cholesterol level of 800 mg/dL?

**DR CLOTET:** The first step should be to confirm the increase in plasma HIV RNA level. A viral load confirmed to be 1000 copies/μL probably represents suboptimal drug regimens, poor drug absorption, or nonadherence to existing regimens. Resistant viral strains can emerge whenever the virus is not maximally suppressed by a particular treatment regimen. However, the low value of plasma HIV RNA together with the high CD4+ cell count in this case probably represents a low accumulation of mutations. A change of therapy is indicated and with the current available drugs (including some new or investigational ones such as adeovir, efavirenz, or amprenavir), we could design a very potent drug combination.

High cholesterol levels such as those seen in this patient are associated with a high short-term risk of coronary artery disease. Although there are active therapies for lowering cholesterol levels when they reach such high values (eg, 800 mg/dL), even with the more active available drugs it is difficult to achieve a complete control of plasma cholesterol levels.

For all the above-mentioned reasons a plasma viral load of 1000 copies/μL is less worrisome than a cholesterol level of 800 mg/dL.

25. What would you recommend for a patient who is taking a 2-nRTI regimen and has a confirmed plasma viral load below levels of detection, but a CD4+ count that increased only to 200 to 300 cells/μL? If the regimen is intensified, is it acceptable to just add an NNRTI or a protease inhibitor without changing the 2 nRTIs?

**DR FISCHL:** Better clinical outcomes are associated with both CD4+ cell count and HIV RNA responses, and progressive increases in CD4+ cell counts with partial immune reconstitution later in therapy have been described with potent antiretroviral therapy that includes a protease inhibitor. Recent data have also shown that there is evolution of the virus toward resistant strains when the HIV RNA level is between 50 and 500 copies/mL. Among patients with decreased HIV RNA responses on 2 nRTIs, assessment of HIV RNA level should be done using a sensitive assay, and if the level is confirmed to be above 50 copies/mL, the regimen should be altered.

For regimens that do not attain suppression of HIV RNA levels to <400 copies/mL within the first 8 to 12 weeks of treatment, intensification with another drug other than an NNRTI may be considered. Recent data suggest that wild-type virus may still be present, reflecting the lack of potency of the initial regimen. However, once HIV RNA levels rebound, the possibility of viral resistance exists and at least 2 of the drugs in the regimen should be changed. Phenotypic assessment of the virus may assist the clinician in identifying the presence of resistant viral strains and identify
which drugs should be avoided.

**Dr Volberding:** Little is known about treatment intensification, although clinical trials are now being designed that should yield data over the next 2 years. Given this patient’s plasma viral load and CD4+ cell count, intensification could be considered but probably isn’t essential. If the plasma virus is below detectable levels by the most sensitive assays available, resistance selection should be minimal and it is not known whether the CD4+ cells would rise with intensified therapy if replication is already minimal. If I were to intensify such therapy, either a protease inhibitor or NNRTI could be used.

In general, I would most readily move to intensification of therapy in a patient with a “good” (at least 0.5 log decrease in plasma viral load) response to therapy but with more than 500 copies/mL after 8 to 12 weeks of therapy.

**26. What is the difference between suboptimal sequential therapy (adding 1 or 2 drugs to a failing regimen) and intensification?**

**Dr Richman:** Adding 1 or 2 drugs to a failing regimen is clearly suboptimal therapy. Patients in whom failure has been established have been shown to have developed resistant virus with increasing likelihood over time of broadened cross-resistance to the class of drugs being used. Why then does the concept of intensification make sense? Recent data suggest that loss of suppression with protease inhibitors may be attributable to outgrowth of wild-type, sensitive virus and that increase in the potency of the regimen by the addition of a single drug to a borderline effective regimen will suppress the replicating virus.

Although there are theoretical and anecdotal data to support this approach, guidelines to help decide whether intensification versus a significant change in the regimen is the wisest course of action cannot be provided with our currently available information.

**Dr Vella:** Intensification means the addition of “another” drug to a regimen that seems quite effective but is unable per se to induce a maximal HIV suppression (e.g., plasma HIV RNA is lowered, but not to below detectable levels when measured with a sensitive assay).

Intensification is an early option, if a potent regimen does not induce a maximal HIV suppression within 24 to 28 weeks, and particularly with patients starting therapy with very high baseline plasma HIV RNA levels.

Suboptimal sequential therapy is the addition of “just” a new drug (instead of the correct strategy to possibly change all drug components) to a previously active regimen that is now failing (e.g., a regimen that induced a good suppression of HIV replication—to below detection level—but, after a variable period of time, begins to fail, as defined by a confirmed detectable plasma HIV RNA).

**Dr Saag:** I would continue with the same regimen. In the context of viral replication being the driving force of disease pathogenesis, the current regimen is achieving near maximal suppression of replication. You can’t do much better than that. Chances are that the CD4+ percentage has actually gone up, but the total white blood cell count or total lymphocyte count has decreased, perhaps due to the regimen itself. In this setting, it is unlikely that the patient will progress clinically even with a stable (nonincreasing) CD4+ count. I would “stay the course.”

**Dr Kuritzkes:** I agree with Dr Saag. There is no evidence that intensifying the regimen for a patient with a plasma HIV-1 RNA below detection limits will lead to an improved CD4+ cell response. It is possible that increases in CD4+ count may yet occur following a longer period of maximal virus suppression. If this patient is taking hydroxyurea, it could explain the apparent lack of CD4+ response as due to drug-induced lymphopenia.

**27. What do you recommend for a patient who begins a potent combination regimen with fewer than 200 CD4+ cells/μL and, despite achieving a plasma viral load below levels of detection (≤50 copies/mL) during the 1-year treatment period, shows no increase in CD4+ cell count. Change, intensify, or continue with the same regimen?**

**Dr Katzenstein:** Intermittent combinations (of 3 or more drugs) have not been evaluated as extensively as many of the nRTIs monotherapies and combinations. In a resource-limited environment where patients may have difficulties in accessing a steady supply of drugs and monitoring, 1 or 2 nRTIs have some advantages over the use of potent anti
retroviral therapy over the short term. The drugs that offer the most prolonged activity in partially-suppressive regimens without the rapid development of high-level resistance are zidovudine, didanosine (with or without hydroxyurea), and stavudine. With protease inhibitors, lamivudine, or the NNRTI drugs (nevirapine, delavirdine, and efavirenz) used in intermittent courses, the selection of resistant strains would be expected, with less effective virus suppression with each “round” of intermittent therapy.

**Dr Clotet:** Intermittent combination therapies could produce the emergence of drug-resistant virus if maximal HIV suppression is not achieved. This will favor the generation of many HIV-1 resistant isolates that could be transmitted, increasing the difficulty in the selection of initial regimens in developing countries. Intermittent therapies will not be cost-effective if they do not maximally suppress HIV-1 replication.

### V. RESISTANCE TESTING ISSUES

29. **Please comment on augmenting or changing a regimen that was started sub-optimally in a patient with a baseline CD4+ count of 50 cells/μL (i.e., zidovudine monotherapy, multiple nRTIs, indinavir added to failing zidovudine/lamivudine). The patient’s plasma viral load is variable between 25 and 750 copies/mL and the CD4+ count is 200 cells/μL.**

**Dr Hammer:** It is difficult to give a single response to this question as the answer truly depends on the options available to the patient. In the case described, a good initial antiretroviral response has been achieved as the CD4+ cell count has risen substantially and the viral load is detectable but low. Thus, the patient is at low risk of near-term clinical progression. In someone who has only taken zidovudine monotherapy, an aggressive approach is reasonable, including 2 new nRTIs such as stavudine/lamivudine, combined with a potent protease inhibitor. In someone who has had multiple nRTI exposure, a dual protease inhibitor regimen combined with an NNRTI such as efavirenz would be a reasonable option if one wanted to be aggressive and try to achieve maximal virus suppression. Alternatively, a more conservative approach would be to follow the patient carefully and defer addition of a protease inhibitor or NNRTI until there is further evidence of virologic failure. In someone in whom a protease inhibitor and nRTIs have failed, the options become more limited. The approach in this circumstance depends on the philosophy of the physician and patient as, for example, one might choose to wait for a greater degree of virologic failure before instituting a switch. However, it is advisable not to wait until the plasma HIV-1 RNA has risen above the 10,000 to 20,000 copies/mL range as it is becoming increasingly clear that the ability to successfully suppress virus in an individual who has experienced failure on a protease inhibitor—containing regimen is inversely related to the plasma HIV-1 RNA level. If one were to initiate a change in someone in whom indinavir/zidovudine/lamivudine has failed, one option would be to employ a dual-protease inhibitor regimen with a change of the nRTIs to stavudine plus didanosine and to consider addition of an NNRTI such as efavirenz. It should be noted that resistance testing may not be helpful in an individual with a viral load between 25 and 750 copies/mL as PCR amplification from the plasma is variable at these low levels, although the technology is continuously improving.

**Dr Fischer:** For patients with advanced HIV disease who had taken nRTIs, adding lamivudine and indinavir provided clinical and survival benefits but did not necessarily result in maximal suppression of HIV replication as measured by both HIV RNA plasma levels and viral culture. Therefore, for the patient with prior zidovudine experience, a new regimen should include 2 new nRTIs, excluding zidovudine, and a protease inhibitor. Alternative regimens with 2 protease inhibitors, such as ritonavir/saquinavir, or an NNRTI, such as efavirenz, rather than a single protease inhibitor may be considered.

A similar philosophy should be used for multiple nRTI experience: a combination of 3 new drugs, ones the patient has never taken and based on treatment history to which the virus is still likely to be susceptible. Phenotyping of the virus may assist the physician in identifying which drugs not to use. Such combination regimens can include nRTIs, NNRTIs, and 1 or 2 protease inhibitors.

Regimens for protease inhibitor failures are more difficult to determine but should include 3 to 4 new drugs, whenever possible, to which the virus is still likely to be susceptible. Again, phenotyping of the virus may assist the physician in
identifying which drugs not to use. Such combination regimens can include a combination of nRTIs, NNRTIs, and protease inhibitors. Preliminary data suggest that regimens that include dual protease inhibitors may be particularly beneficial.

30. How does genotype correlate with the phenotype? Which is the better clinical predictor of drug failure?

**Dr Brun-Vézinet**: According to the data presented at the HIV Drug Resistance Workshop in June 1998, the correlation between genotype and phenotype is better for HIV-resistant isolates than for sensitive strains. Several genotype-phenotype databases are currently in development with the aim of generating software that can predict phenotype from genotype results. Retrospective studies reported that baseline genotype and/or phenotype may predict the viral load response in patients who had previously experienced several therapeutic failures. For example, Lanier et al showed the predictive strength of baseline genotype and phenotype in abacavir-treated patients. Zolopa and colleagues demonstrated that genotype at baseline is a strong predictor of virologic response in patients receiving ritonavir/saquinavir after a previous protease inhibitor-containing regimen failed. In this study the genotype data had a better predictive value than clinical and drug history. It is not known at the present time whether genotype or phenotype is the better predictor of drug failure. Finally, the utility of phenotypic and genotypic testing in HIV-infected patients must be evaluated and validated through prospective studies.

31. Has the clinical role of genotyping and phenotyping testing changed in any way from data presented here at the Geneva conference and at the Drug Resistance Workshop in June?

**Dr Loveday**: One important conclusion from these two recent conferences was that there is an urgent need for the generation of a database(s) that documents genotype, phenotype, and clinical outcome for thousands of patients so that relationships may be analyzed to assist in understanding the use of these measures in clinical care. However, based on results of clinical studies at these meetings and unpublished data I have seen since, our center in the United Kingdom has determined to include real-time genotyping as part of our management for the best care of our patients. I now feel that failure to test may, in some cases, result in ineffective therapies and a wasteful use of drugs. We will not be able to answer all the questions at this time, but if we can prevent patients who are drug-naive or undergoing their first change in therapy from starting an inappropriate combination—one to which they are doomed to become unresponsive—we are making enormous clinical strides.

The economics of this philosophy are simple: it costs the price of approximately 2 months’ supply of 1 drug to test for resistance to all drugs in 1 patient, and this simple expedient could save thousands in wasted therapy over the following year.

32. Is drug-level monitoring currently useful? If not, do you expect it to be useful in the future?

**Dr Yeni**: There is no clear demonstration that drug-level monitoring is useful in the clinic. However, on an individual basis, it may be useful to confirm that plasma concentrations are in the therapeutic range, especially when drug pharmacokinetic interactions are expected to occur. The approximation in the pharmacokinetic characteristics, when assessed by 1 blood sample only, must be recognized and complicate the interpretation of the result, even if the exact time of the last drug dosing in the patient is recorded. Drug-level monitoring is not adequate for assessment of adherence, because of the risks of overinterpretation of a result from a single determination.

**Dr Kuritzkes**: At present, therapeutic drug-level monitoring is not recommended for monitoring antiretroviral drugs. In the case of nRTIs, the half-lives of the drugs are too short to use trough levels as a meaningful marker of adherence to treatment. Moreover, it is the level of intracellular dideoxynucleoside triphosphate that really matters.

In the case of the NNRTIs and protease inhibitors, drug-level monitoring may be useful in very specific cases where some unusual drug-drug interaction is suspected. In such cases an in-patient pharmacokinetic study could be performed in which serial measurements are obtained after an observed dose of drug is given.
33. It has been noted that "the measurement of detectable viral RNA reflects ongoing infection." How does this correlate when viral genomic RNA is a consequence of host cellular v-RNA production from integrated proviral DNA, and does not have anything to do with infection?

Dr Richman: Plasma HIV RNA is full-length genomic RNA present in intact virions produced by infected CD4+ lymphocytes in lymphoid tissue. In the lymphoid tissue of untreated patients or patients treated with nRTI-only regimens, the RNA present is predominantly of the same composition. With potent therapy that results in plasma levels of HIV RNA of <50 copies/mL, the RNA changes its distribution and character with much of it representing multiply-spliced transcripts. The mechanisms involved in these changes have not been well characterized.

34. You spoke of an increased risk of virologic failure with a large recovery of CD4+ cell count. Can you comment on the dampened increase in CD4+ cell count seen with hydroxyurea in light of this risk factor? Is this potentially a contributing factor to HIV benefit?

Dr Richman: ACTG 343 showed that the patients with the greatest elevations in CD4+ cell counts (which is probably very encouraging immunologically) may paradoxically provide more potential host cells for outgrowth of suppressed HIV. Regimens with borderline activity may fail despite the greatest elevations in CD4+ cell counts. Theoretically this situation may benefit from the suppressive effects of hydroxyurea on CD4+ lymphocytes. Studies are in progress to examine whether diminishing CD4+ cell activation with hydroxyurea will help suppress viral replication in these patients.

35. Could genotypic or phenotypic testing results be used as a reason for changing therapy in the absence of evidence of virologic, immunologic, or clinical failure?

Dr D'Aquila: I would not change therapy if genotypic changes or phenotypic resistance was detected when plasma HIV RNA levels remained adequately suppressed. Resistance tests rely on an initial PCR amplification step, which can be prone to cross-contamination in the laboratory and lead to a risk of a false-positive result. I would not order resistance testing unless there was evidence of virologic failure. In my view, virologic failure should be the trigger for when to change therapy and it will almost always precede immunologic or clinical failure. I define virologic failure as confirmed lack of an adequate decrease in HIV RNA within the first month or two after starting therapy, confirmed lack of suppression to below detectable levels (<50 copies/mL) after 6 months or more of therapy, or a confirmed rise of greater than 4-fold in plasma HIV RNA levels at any time. If any of these criteria are met, I would change therapy whether or not immunologic or clinical failure was evident and whether or not resistant virus was present. Detection of virus resistant to a drug may suggest which drug(s) should not be used in the next regimen, but it should not be used to indicate when to change therapy.

Dr Clotet: The absence of evidence of virologic failure means that a patient has plasma HIV-1 RNA levels below detection (ie, <200 copies/mL). Generally, plasma HIV RNA samples with more than 1000 copies/mL are needed to generate genotypic and phenotypic results. Resistance testing is not likely to be useful when values are below this level. For this reason, in the absence of virologic failure, genotypic or phenotypic testing cannot be used for guiding the change of therapy.

Genotypic and phenotypic testing should be used in a setting of virologic failure (HIV RNA >1000 copies/mL) in spite of the absence of immunologic or clinical failure.

Currently, phenotypic assays are becoming widely available. Phenotypic assay manufacturers are building databases relating findings from their test to later outcomes. The information generated will be very useful for selecting alternative regimens in case of virologic failure.

36. Do you recommend genotyping or phenotyping prior to changing medications or starting medications if plasma viral load is >1000 copies/mL?

Dr Brun-Vézinet: In patients with primary infection, therapy must be started without any delay. But in settings where surveillance studies have demonstrated that 5% or 10% of virus isolates...
have resistance mutations, I would recommend performing genotypic testing on the first available plasma specimen. The results could help to define a better therapeutic strategy. In patients with long-term, evolving HIV infection, drug-resistant variants transmitted during primary infection may be difficult to detect in the absence of therapy because wild-type strains will have a replication advantage. In patients in whom therapy is failing, several retrospective studies support the predictive value of genotypic and phenotypic testing on a subsequent viral load response to an alternative therapy. However, these results require validation through prospective studies. There is evidence from existing data that phenotype or genotype analyses will have a role in the clinical management of HIV-infected patients. It is possible that they will have different utilities according to the drug history and the number of previous drug failures.

Dr. Kuritzkes: Unlike plasma HIV-1 RNA, which reflects the actively replicating pool of virus, proviral DNA is largely constituted by archival viral sequences—that is, the DNA record of virus that was actively replicating at some time in the past. Equilibration of sequences between plasma and cellular (proviral) compartments is variable, ranging over weeks to months. The chief concern would be that failure to observe an expected resistance mutation in proviral DNA does not guarantee its absence from the actively replicating pool of virus. Personally, I would prefer to obtain a virus isolate by culture for sequencing, since there is more rapid equilibration between plasma HIV-1 RNA and activatable PBMC-associated virus compared with the total proviral DNA pool.

Dr. Loveday: There are two aspects to this question. First, although plasma viral load should be more than 1000 copies/mL to obtain genotypic information and most approaches have been quoted as needing this level of plasma virus, new advances are occurring rapidly in the genotyping technologies. Since at least some approaches are asking for 500 copies/mL or even less, matters are likely to progress rapidly in this area. Second, we and others have demonstrated that proviral DNA can be used to determine information about genotypic changes associated with resistance, and our experience is that it probably reflects the plasma picture that existed 2 to 4 weeks previously. To answer the question directly, it is an approach we frequently use when having trouble with low plasma viral load.

Dr. Hammer: In general the “staging” of HIV disease has become less meaningful over time with the recognition that the disease process is a complex continuum. A better and more useful term is “characterization” of where an individual stands in that continuum. Currently, the presence or absence of symptoms, the CD4+ cell count, and the plasma HIV-1 RNA level are used to characterize where patients stand prognostically. If the question is suggesting that perhaps resistance testing should be added to the characterization of patients, it is a most intriguing proposition. The greatest use of these assays ultimately will be in helping to choose an appropriate antiretroviral regimen in circumstances such as a newly diagnosed patient who is at risk for having acquired a drug-resistant strain or in someone experiencing virologic failure on a current regimen. In these circumstances, the characterization of the patient at the start of therapy or when considering a change in therapy would be enhanced, thus leading to greater individualization of treatment, which is an important goal. Although early studies demonstrated that phenotypic and genotypic evidence of resistance to zidovudine were independent predictors of clinical outcome, whether this is the case in the more complex environment of combination therapy and routine viral load testing is unclear.

Dr. Richman: The roles of CD4+ cell counts and levels of plasma HIV RNA are well established and will not be displaced by assays for drug resistance. We know that risk factors for poor response to antiretroviral drug treatment include high plasma HIV RNA level, low CD4+ cell count, and drug-resistant virus, in addition to poor adherence and other pharmacologic factors that diminish plasma levels. The very important practical questions are whether assays of drug resistance will improve therapeutic results, which assays should be used, and how should they be used. Once again, data are being rapidly accumulated in this rapidly evolving field.
VI. POSTEXPOSURE PROPHYLAXIS

39. Is the delivery of post-sexual exposure prophylaxis achievable and cost-effective?

DR FISCHL: The efficacy of postsexual exposure prophylaxis has yet to be determined and will be influenced by the relative risk of acquiring HIV infection in this setting.

When the risk is relatively low, the demonstration of benefit may be difficult. In addition, the role of postsexual exposure prophylaxis is more difficult to define with repeated sexual exposures to HIV. However, there are enough data related to the prevention of perinatal transmission of HIV and health care worker exposure to assume that in the case of a maximal-risk sexual exposure, prophylaxis with combination antiretroviral therapy should decrease the relative risk of infection with HIV.

DR VOLBERDING: There is no reason to think that prompt antiretroviral therapy following sexual exposure to HIV will not reduce the risk of infection. The problem is that so many other issues need to be considered in such situations. Often, data on the actual risk (is the partner known to be HIV infected, for example) are not available. And the risk may be a recurring one.

Ideally, such treatment should be offered in a setting where data are being collected and where the primary purpose is one of exposure prevention, not postevent prophylaxis.

40. Would you recommend postexposure prophylaxis for a person who has just had sexual contact with someone in whom HIV infection is highly suspected but not confirmed?

DR CONWAY: In this context, a person at high risk of HIV infection but who has not yet been diagnosed as such should be considered to be infected until proven otherwise. Thus, postexposure prophylaxis to protect against the potential transmission of HIV should be offered to the person who is being evaluated. This is particularly true if the presumed “index” case is male, if a condom was not used, or if genital lesions (particularly ulcerative lesions) were present on either partner. A particular situation may relate to the index case having been recently infected. In such a case, the viral load in genital secretions may be quite high, further increasing the risk of transmission of HIV. This being said, the postexposure prophylaxis to be used may be kept quite simple, as the individual transmitting HIV infection is presumably drug-naive and is unlikely to be carrying drug-resistant strains. To date, the only drug to which a significant prevalence of primary drug resistance is reported is zidovudine, and it may be best to avoid the use of this agent in this context. If therapy is initiated, it could be discontinued if the index case has a negative antibody test for HIV infection and acute or early HIV infection can be reasonably ruled out on clinical or laboratory grounds.

DR D’AQUILA: This is a difficult question to answer in the abstract, and it does not become any easier when facing an actual patient. My inclination is to say that the appreciable risk of adverse effects with antiretroviral regimens precludes prophylactic treatment unless the sexual contact is confirmed to be HIV-infected. However, the only alternative approach I could offer to such a potentially exposed patient (who would certainly be quite anxious) is to closely follow repeated plasma HIV RNA levels over the next few months and treat primary infection aggressively if it is detected. But I suspect many patients would not be satisfied with that approach. Thus if I were confronted with a compelling situation about a high-risk sexual exposure to HIV from a person who was suspected, but not proven, to be infected, I might indeed respond to a request for prophylaxis with information about adverse effects and a prescription for a potent combination.

41. Do you believe that in 1998, less than maximally suppressive postexposure prophylaxis should be recommended? Centers for Disease Control and Prevention has dual nRTI as options, but many other guidelines (UK, IAS–USA) do not.

DR HIRSCH: Determination of the actual exposure risk in an individual situation is very difficult. In my view, once the decision has been made that a risk for significant exposure exists, maximally suppressive regimens should be employed. These might involve 2 nRTIs plus 1 protease inhibitor, or 2 nRTIs plus 1 NNRTI. Although these choices will be more costly and potentially toxic than less aggressive regimens, they should provide the
maximal prophylactic benefit currently possible.

**Dr Saag:** “Maximally suppressive” is a term used in the setting of an established infection, with high-level, ongoing replication throughout the body. In that setting, maximally suppressive regimens are required to yield the best opportunity to limit clinical progression and delay or prevent the development of resistance. In the case of postexposure, replication (if it is to occur) is restricted initially to a single location in the body at relatively low levels. The objective is to prevent uninfected cells from becoming infected. Cumulative data from animal model experiments, basic science, natural history, and treatment intervention studies suggest that the “virologic hurdle” to establish infection in the setting of an acute occupational exposure is quite high. As an example, meaningful protection from infection can be achieved with the use of relatively “weak” treatment regimens (e.g., zidovudine monotherapy). Therefore, the use of dual nRTI therapy, or other nonmaximally suppressive regimens, may be appropriate in certain settings (e.g., low-inoculum exposures and exposures from antiretroviral-naive source patients).

**Dr Yeni:** In the case of high-risk occupational exposure and a source patient with unknown HIV serostatus but a risk for infection or with clinical or biological symptoms suggestive of HIV disease, immediate maximally suppressive prophylaxis of HIV infection should be given to the health care worker. If there is no argument for HIV infection in the source patient, prophylaxis may be considered in the case of massive exposure, and must be discussed on an individual basis. The results of a rapid HIV test in the source patient will dictate the health care worker follow-up. The risks of transmission of other infectious agents (particularly hepatitis B and hepatitis C viruses) should also be considered.

### VII. Perinatal Transmission Prevention

**Question 43. A pregnant patient is on an effective potent regimen that includes stavudine. If that patient is intolerant to or has had significant exposure to zidovudine, would you still use zidovudine intrapartum, especially given the recent information about the long-lasting antagonism?**

**Dr Hirsch:** I would not use zidovudine and stavudine concurrently in any patient because of the proven antagonism between these drugs. Although zidovudine is the only drug that is well-established in the reduction of maternal-newborn HIV-1 transmission, I doubt that there is any magic to zidovudine in this regard. If the virus is well-suppressed in the mother using a regimen that appears safe in pregnancy, I would continue that regimen. One might consider replacing stavudine with zidovudine in the newborn during the first few weeks of life.

**Question 44. What is the recommendation for prevention of perinatal transmission in pregnant women whose virus has the 215 reverse transcriptase mutation or who is intolerant of zidovudine?**

**Dr Schooley:** At this point there is little evidence that there is anything “magic” about zidovudine in the prevention of perinatal transmission. As the data have emerged, it appears that the key points are employing a drug regimen that has an impact on plasma HIV RNA levels in the mother and having 1 or more antiretrovirals that are active against the potentially transmittable virus in the neonate. In developing the mother’s regimen, it is further important that care be taken not to limit her own therapeutic options downstream by placing her on a regimen that allows viral replication in the presence of selective pressure. Thus, in a case such as this, I would be quite comfortable crafting a regimen in the mother that is likely to drive plasma HIV-1 RNA levels below detection and choosing a nonzidovudine-containing regimen for the immediate perinatal period for the child. This is a rapidly changing area with respect to available formulations and it is best approached by working closely with a pediatrician who is facile with the use of antiretroviral drugs in the perinatal period.
**Dr D'Aquila:** A role for resistance testing still needs to be defined for this situation and validated in any setting, but I would likely use resistance testing as I would in any patient in whom a regimen is failing. Current knowledge does suggest it is best for both the woman and the fetus to optimize HIV suppression. If plasma HIV RNA was low and stable (eg, <1000 copies/mL, but detectable), I would not recommend resistance testing. I might try intensification with 2 additional drugs this patient had never used that were not expected to share resistance patterns with any previously used drug. If the plasma HIV RNA level were higher or rising, I would still not order resistance testing as a first step. I would first try to choose a 3- or 4-drug regimen that included drugs that had not previously been used and to which cross-resistant virus was not expected to have been selected by any prior regimen. I would likely recommend 4 drugs if the viral load was higher than about 250,000 copies/mL. If prior antiretroviral experience was so extensive that this was not possible and plasma HIV RNA was below 1000 copies/mL, then it would be reasonable to attempt drug resistance testing to help choose the next regimen from a list of previously used or cross-resistant drugs. However, the available data indicate that resistance test results predict failure of a resistant drug much better than they can predict the success of a drug to which the patient's virus tests as susceptible. Major reasons for this include the technical lack of detection of a minority of resistant virus that might be selected in vivo by re-introducing the old drug and the possibility of drug failure through mechanisms other than drug resistance. Thus, I would use the resistance test results only to exclude drugs that were very unlikely to work.

**Dr Conway:** The specific goal of antiretroviral therapy in pregnancy is to reduce the risk of transmission of HIV from the infected mother to the unborn child. As such, it may be important to optimize therapy to reduce circulating viral load as much as possible, as this has been associated with a reduced risk of transmission. In this context, resistance testing may be helpful to evaluate if genotypic mutations conferring decreased susceptibility to the agents the mother is currently taking may have developed. This may allow for optimization of the regimen to include 3 drugs to which the viral isolates are sensitive. The evaluation of resistance to agents the mother may have taken in the past would not yield reliable results, as resistant isolates may not be present in sufficient numbers to be detected, but may rapidly emerge if a specific drug were restarted. Similarly, it could be assumed that the viral isolates are susceptible to drugs the mother has never taken as long as no cross-resistance is known to exist between such drugs and any other(s) to which she may have been exposed.
VIII. HEPATITIS COINFECTION

47. In patients with HIV disease, CD4+ count >200 cells/μL and plasma viral load <10,000 copies/ml, hepatitis C- or hepatitis B-positive, and with liver disease/failure, should we evaluate for liver transplants as in non-HIV-positive patients?

Dr Richman: Chronic hepatitis B and C infections are increasingly confounding HIV patient management, especially with regard to the use of protease inhibitors. Issues of risk-benefit and health care utilization of liver transplants in HIV-infected patients are very complicated. I believe that the advisability of this as a process merits the consensus deliberations of a number of experts. The risk and expense of such a procedure with the very limited availability of organs requires much thoughtful input.

Dr Volberding: The most common cause of liver damage necessitating transplantation in the United States is hepatitis C virus infection. This infection is extremely common in patients with HIV infection. Most transplant centers reject those with HIV coinfection given the presumably real risk of acceleration of HIV disease associated with transplant-related immune suppression. Some centers are beginning to consider such procedures, which I believe can be appropriate given our current ability to control HIV replication. In many patients, death will result from hepatic failure well before HIV disease progresses to advanced stages. Certainly, the potential risks of this need to be considered, but I do not favor an outright prohibition.