

# INITIAL (ESTABLISHED) INFECTION

## INITIATION OF ANTIRETROVIRAL THERAPY: WHEN TO START

**9. If HIV RNA determinations are not available, what are the recommendations for treatment for persons who are asymptomatic and have recent documented seroconversion (<6 months, from a negative test)?**

**Dr Katzenstein:** The recommendations for the initiation of therapy are not based on knowledge of the time of acquisition of infection, but on clinical trial data and the use of laboratory and clinical indications for treatment. The fraction of subjects with less than 6 months of infection who are very rapid progressors may be best defined by measurement of plasma HIV RNA; subjects with greater than about 50,000 HIV RNA copies/mL are most likely to develop clinical AIDS within 1 to 2 years. In addition, observational studies suggest that a history of a severe or prolonged seroconversion illness, a rapid and sustained decline in CD4+ cells, or the early appearance of minor clinical symptoms (particularly oral candidiasis, unexplained weight loss and fever, oral hairy leukoplakia, or persistent herpes simplex virus infection) predicts a greater risk of clinical progression.

There are few data available that would alter the current recommendations based on a known time of seroconversion. One or more of the above findings, a CD4+ cell count persistently below 500/ $\mu$ L (or one that is declining rapidly or a CD4+ percent <15 to 20) or symptoms of immunodeficiency should prompt initiation of antiretroviral therapy.

**Dr Volberding:** Plasma HIV RNA assays are rapidly becoming available and should be considered for routine HIV disease management. For patients with long-standing infection, the HIV RNA level helps estimate prognosis and is also useful in guiding decisions about initiating and changing antiretroviral therapy. For primary HIV infection, the value of the plasma HIV RNA titer is somewhat less clear, although information is rapidly becoming available. The peak plasma HIV RNA titer is probably less important than the level after 6 months (the "set point") and treatment may be recommended regardless of the plasma HIV RNA level. Still, it would seem important to know the starting titer to determine whether therapy was at all (or still is) beneficial. If the plasma HIV RNA titers are truly unavailable, treatment should be initiated with response assessed by clinical evaluation and CD4+ cell counts as described above.

**10. Do lymphoid tissue analyses have any place in determining when to treat early established disease?**

**Dr Volberding:** The lymphoid tissue (nodes, tonsils, spleen, etc) are considered the primary site of HIV replication. These tissues also contain nonreplicating "trapped" viral particles. In general, the virus produced in those tissues is easily and rapidly passed into the plasma compartment and the plasma HIV RNA level reflects the number of infected cells in the lymphoid tissue. Analyses of lymphoid tissues, therefore, are probably not necessary in deciding when to treat or when treatment needs to be altered. Lymphoid analysis is an important research tool, especially in settings such as acute HIV infection, where one might evaluate whether aggressive antiretroviral therapy has eradicated HIV from the body. Again, this analysis is a research tool only at present. Various means are being investigated including fine needle aspiration, true-cut needle biopsy, and incisional and excisional surgical removal. The CD4+ cells are not randomly distributed within a node, so an overall node CD4+ cell count is probably not of relevance.

**Dr Richman:** The examination of lymphoid tissue is an important area for investigation; however, sufficient data have not been generated to guide patient management.

**11. How soon until sufficient studies are completed for the panel to reasonably recommend "hit early-hit hard" as the best strategy?**

**Dr Katzenstein:** Definitive studies of early ("hit early-hit hard") treatment strategies will require many years to complete and are unlikely to produce clinical endpoint data for at least 5 years. Recent studies of natural history in gay men (MACS) and in persons with hemophilia show that the median time from seroconversion to development of AIDS is about 8 years. Even patients with elevated plasma HIV RNA levels have a median time to onset of AIDS of more than 4 years. Since it will be very difficult to conduct placebo-controlled studies among patients at highest risk, studies are likely to compare intensive (3-drug regimens including a protease inhibitor) with less intensive (two-nucleoside) regimens. While these may yield important CD4+ count and plasma HIV RNA data within the next 2 years, the long-term benefits will take much longer to assess. Currently planned studies that will "hit early and hard" for 1 to 2 years followed by withdrawal or reduction in intensity of therapy will test the hypothesis that the viral "set point" can be changed by aggressive therapy.

The key data that will allow a "hit early-hit hard" strat-

egy will rely on the completion of a treatment trial that enrolls a sufficient number of patients at risk of progression, follows them on combination therapies, demonstrates continued suppression of viral load, and shows that the risk of clinical endpoints is much lower than the risk estimated by recent natural history data.

**Dr Volberding:** The Panel largely adopted a "hit hard, hit early" strategy. It discouraged the use of monotherapy and considered complete viral load suppression as a reasonable goal. We recognized that ongoing replication in the face of partially suppressive therapy will lead to overgrowth of resistant viral populations and that combinations appear able to delay or prevent resistance, presumably through more complete viral inhibition. All of that said, we did not feel that we knew whether each HIV-infected person will need the specific combination of nucleosides and protease inhibitors immediately regardless of clinical stage, CD4+ cell count, or plasma HIV RNA level. It seems conceivable that longer-term treatment strategies selectively deploying all available drugs will prove necessary.

## WHAT TO START WITH: NUCLEOSIDES AND PROTEASE INHIBITORS

### 12. Please address the issue of initiating nucleosides alone or in combination with a protease inhibitor?

**Dr Katzenstein:** With respect to the initiation of nucleosides, the panel views the clinical results for zidovudine/didanosine, zidovudine/zalcitabine, and didanosine alone as convincing, and the marker data (HIV RNA and CD4+ changes) for zidovudine/lamivudine and didanosine/stavudine combinations as strongly suggestive that these are potent regimens. Recently, clinical endpoint data for zidovudine/lamivudine to further support its use in initial regimens have become available. In addition there are preliminary virologic endpoint data for stavudine/lamivudine to suggest its possible role in initial regimens for patients who cannot tolerate zidovudine.

A current decision is whether to initiate didanosine, 2 nucleosides, or 2 nucleosides plus a protease inhibitor. Because the clinical data for nucleosides indicate clear superiority of nucleoside combinations or didanosine over zidovudine monotherapy, they are recommended for all patients in whom therapy is considered. Physicians may be inclined to use specific combinations based on their experience and comfort with the drugs, patient preferences for specific dosage formats and timing of doses, and the potential for increased toxicity with zidovudine-containing regimens.

The addition of a protease inhibitor to an effective initial nucleoside regimen should be strongly considered for patients who are at increased risk of progression based on

their plasma HIV RNA level, CD4+ cell count, or both. Protease inhibitor monotherapy thus far has been a disappointing approach to initial therapy and is even less likely to provide a sustained decrease in viral load in patients with a history of prolonged nucleoside therapy. Thus, protease inhibitors should always be given with at least one, and if possible, two nucleoside RTIs.

### 13. What is your "gold standard" for anti-retroviral combination therapy against which we should judge future drugs or drug combinations in patients with CD4+ cell counts >350-500/ $\mu$ L? What about ongoing studies that don't reach the standards of the recommendations?

**Dr Katzenstein:** The "gold standard" at this point in time for patients in this range might be considered to be any drug combination that results in a maximal reduction in plasma HIV RNA levels and a rise in CD4+ counts with a minimum of side effects and toxicities. Complete suppression of plasma HIV RNA, as currently defined by below the limit of detection of the assay (<200 copies/mL), has been achieved in some patients receiving certain 2- or 3-drug combinations. It may be reasonable to conclude that complete suppression of plasma HIV RNA is a new benchmark that should always be sought, but there are little data on the safety, feasibility, or value of maintaining complete suppression of HIV RNA for more than 48 weeks.

There are several caveats to complete suppression strategies and regimens. First, it is not clear that suppression of detectable HIV RNA in the plasma accurately reflects absence of virus replication in cellular compartments. Second, multidrug regimens may result in the induction of drug-resistant virus, particularly if excellent adherence with each drug cannot be sustained. Inadequate compliance with drug regimens may result in the development of multidrug resistance, making the question of adequate drug levels in all tissue compartments very important. Thus, while the early use of combinations halts some of the pathogenic processes in HIV infection (notably CD4+ cell decline), early use of potent suppressive combinations may close off options to the use of the drugs later in disease. Third, the cost benefits of early aggressive therapy are difficult to determine. Asymptomatic patients with relatively low plasma HIV RNA levels are at little risk of disease progression over 2 to 3 years, since the incidence of AIDS in patients with less than 5000 copies/mL and a CD4+ cell count greater than 350 cells/ $\mu$ L is less than 2% per year (based on data from the ACTG 175 and the DELTA studies). Drug costs of more than \$10,000 per year and a reduction in the quality of life experienced by asymptomatic patients taking two or three potent anti-retroviral drugs may outweigh the theoretical advantages afforded by complete suppression. Since, as far as we know, it may be necessary to continue drug treatment

indefinitely, it is crucial to ask whether the patient is willing to sustain such a regimen over the long term.

For patients with an immediate risk of AIDS or death, (ie, those with the highest HIV plasma RNA levels and low CD4+ cell counts), aggressive therapy to achieve the maximum reduction in HIV plasma RNA appears to be warranted. On the other hand, studies examining regimens that may maintain low, but detectable levels of virus replication are critical because they may demonstrate an equal or greater long-term benefit with better compliance, less risk of drug resistance, and a better quality of life. Reduction in plasma HIV RNA reduces the immediate risk of AIDS; however, once the risk of disease over the ensuing 2 to 3 years approaches zero, our ability to project long-term survival is still quite limited.

**Dr Volberding:** It is quite difficult to use the term "gold standard" when things are changing as quickly as they are in HIV management. It is also hard to focus on a specific CD4+ cell range when our current thinking is dominated by considerations of plasma HIV RNA titer. All that aside, the ideal antiretroviral therapy would effect a complete suppression of viral replication in all tissues with minimal side effects. It would also be easy for the person to take (once or twice daily without strict dietary limitations) and would be inexpensive. It would be durable in its benefit and not interfere with other necessary drugs or limit the subsequent use of other antiretroviral drugs. Although such a treatment has yet to be developed, it is important to keep these considerations in mind as standards with which given treatments can be compared. The difficult question is which element of this standard is most critical. Obviously, an extremely potent drug that is too toxic to take is of no value. Nor is a cheap, nontoxic drug if it does not inhibit viral replication.

**14. In planning a strategy with combination antiretroviral therapy, does order matter? For example, if zidovudine/lamivudine is used first, do we need to worry about cross-resistance to didanosine or stavudine?**

**Dr Volberding:** The order of therapy certainly matters. If possible, initial drugs should be chosen that don't "use up" later options by leading to drug-resistant mutations that cross over to a drug that could prove useful later in treatment. This said, there are few convincing data on clinically significant phenotypic cross-resistance. Also, other considerations including drug potency and tolerability may outweigh theoretical concerns of cross-resistance.

The Panel, in considering this issue, noted that the initial use of lamivudine may limit subsequent use of didanosine or zalcitabine. Also, as commented earlier, initial use of indinavir or ritonavir may limit later effectiveness of current protease inhibitors. Again, this is not to suggest, for the other considerations mentioned, that one is wrong

to use lamivudine, indinavir, or ritonavir as a component of initial therapy. This is an area of HIV medicine where substantial new information is expected to become rapidly available.

**15. In the light of the clinical endpoint results of the Concorde trial, is the enthusiasm for the protease inhibitors justified?**

**Dr Saag:** The results of the Concorde trial have to be placed in the context of our current understanding of HIV pathogenesis. From a pathogenesis perspective, zidovudine generally is effective for 6 to 12 months as monotherapy. Therefore, for more than two thirds of the 3.5 years of follow up in the Concorde, patients were, in essence, on ineffective therapy, compared with those individuals who received their 6 to 12 month benefit a little bit later. Ultimately, all of the patients, whether treated early or delayed exhausted the clinical benefit of zidovudine therapy. This information is not applicable to the current approach to treatment, which individualizes therapy based on the patient's level of viral replication. Moreover, the protease inhibitors, especially when used in combination with other agents, achieve antiretroviral effects that are 50 to 500 times more effective and are more durable. In this regard, the enthusiasm for the protease inhibitors is well justified.

**Dr Vella:** The results of the Concorde trial have to be interpreted as a demonstration that an incomplete inhibition of viral replication is not able to modify in the long term the natural history of the disease. What has been seen in the Concorde trial cannot be looked at with the same perspective as the results of the recent triple combination studies. Indeed, now that relevant and sustained decreases of viral replication have been proven to be associated with a better outcome (mainly through the virological data from the DELTA and ACTG 175 trials), the results that may be obtained with protease inhibitors in combination with RT inhibitors can be seen as really encouraging.

**16. In Europe and Australia 15% to 25% of patients with HIV disease are infected with zidovudine-resistant virus. As a general rule, do you still recommend initiating therapy with zidovudine-containing regimens?**

**Dr Volberding:** The issue of the prevalence of viral resistance to antiretroviral drugs in untreated patients is still far from settled. In the Delta 1 study, about 6% of subjects had RT resistance mutations; in unpublished data from San Francisco General Hospital, patients who were the source of needlestick occupational injuries rarely had either zidovudine or lamivudine resistance mutations. Little if any data are available on the prevalence of phenotypic resistance but it is presumed to be even less common.

While some data show a high prevalence of RT resistance mutations (up to 13% in ACTG 175 study, for example), this information is not currently a key variable in the choice of initial drugs. As the clinical relevance of genotypic resistance becomes understood and assays to measure genotypic resistance become available, and more patients in the community are treated with multiple antiretroviral drugs, choosing strategies based on resistance patterns may become routine.

**Dr Richman:** The prevalence of zidovudine-resistant strains in recently infected patients in the developed world appears to be less than 10%, and is probably closer to 5%. These rates do not preclude the use of zidovudine-containing regimens. With more data, alternative nucleoside regimens may prove to be reasonable or even better strategies. In the meantime, the plasma HIV RNA response is one way to assess adequacy of a regimen. Satisfactory phenotypic or genotypic assays for HIV drug resistance have not yet been developed for individual patient management.

### **17. Why not initiate therapy with the most potent antiretroviral combinations that from data presented seems to require inclusion of at least one protease inhibitor?**

**Dr Volberding:** It is difficult to argue that a less potent antiretroviral strategy should be used in place of a more potent one. However, if the goal is to achieve effective control of HIV replication, it may be possible to do so with less aggressive therapy, at least in some patients. If so, the cost, toxicity, and compliance issues raised by more aggressive combinations might be forestalled, or even avoided. Also, it seems likely from current clinical experience that some patients will not achieve complete HIV suppression, even with protease inhibitor-containing combinations. This is a centrally important issue in the field of HIV medicine. While complete HIV suppression is an extremely attractive goal, it remains to be proven that the effort required to achieve this will be superior to less stringent approaches in all patients and at all stages of HIV infection.

**Dr Vella:** Results recently obtained with triple combination therapies indeed induced a wave of optimism among clinical researchers and among persons living with HIV infection. A concept that a few months ago could have been seen as merely provocative—HIV eradication—is emerging as a testable hypothesis, with mathematical models suggesting that after some years of theoretical zero replication, HIV infection may even burnout as chronically infected cells die off.

However, a reduction of the plasma viral load below assay level of detection does not necessarily mean that HIV is absent from the body. Data are also insufficient to say how long it takes for HIV to re-emerge despite continued treatment. Although it is now generally accepted that an

undetectable plasma viral load is a reasonable goal, even with highly effective regimens this target is not achievable in all patients. Also, theoretically, resistance may occur even at "zero" plasma viral load, because some level of replication may still be ongoing in reservoir or sanctuary sites and resistance mutations may pre-exist before therapy starts. This last issue is one of the most compelling reasons for treating early and aggressively: with viral variation beginning with the first replication cycles during primary infection, earlier initiation of therapy would be expected to result in a more durable response than would be expected in the later stages of HIV disease, when a broader array of drug-resistant mutants would be expected to be present. Further, patients who will benefit the most from antiretroviral therapy are most probably those with less-advanced disease, before irreversible immunologic damage has occurred.

All of these considerations must be weighed, however, against a number of other issues that include compliance, tolerability, accessibility, and the still unknown long-term effects. Moreover, the strategy may differ according to the different virologic and immunologic status of the patient. For some patients (ie, those with low plasma HIV RNA levels), initial therapy with a combination of RT inhibitors may reduce plasma HIV RNA levels below detectability, while for others a more aggressive therapy may be desirable.

**Dr Montaner:** It is important to emphasize, in this context, that what we currently measure as "suppression of viral replication" (ie, HIV-1 RNA below the limit of detection of the assay) is most often partial rather than full suppression of viral replication. This represents a major limitation of current therapeutic strategies as we remain uncertain of the potential incremental gain of treating beyond non-detectable levels in an aim to achieve a true full suppression of viral replication. Of note, this limitation will only be partially addressed by the newer generation assays, which still have a lower limit of detection in the range of 20 copies/mL.

### **18. Double nucleoside therapy inevitably will lead to residual viral replication, eventually leading to loss of antiretroviral efficacy of the drugs. When do you recommend the initiation of triple-combination therapy? On what criteria?**

**Dr Volberding:** Unless permanent and complete suppression of HIV replication is achieved, overgrowth of pre-existing clones of resistant virus seems ultimately unavoidable, regardless of the number of agents employed or their target in the viral life cycle. As discussed elsewhere, it may prove over the longer term course of the patient's infection, appropriate to employ less aggressive combinations, particularly if the pretreatment HIV RNA titer is relatively low. The central issue probably has less to do with

how many drugs are used and more to do with how effective the drugs chosen are in inhibiting HIV replication sufficiently to achieve substantial clinical benefit and to delay the loss of effect caused by viral resistance.

**Dr Katzenstein:** Double nucleoside therapies can result in suppression of viral replication below the limits of current detection systems in up to 20% of subjects treated in early disease. Thus the maxim that 3-drug regimens that include a protease inhibitor or an NNRTI are required to achieve complete suppression of viremia may not be completely accurate. The inevitability of resistance to 2 nucleosides with subsequent virologic failure is also not documented. Many patients have been maintained on zidovudine/didanosine for more than 4 years without a return in virus load toward the pretreatment value or the detection of drug-resistance mutations (215 and 74, respectively). The strategy of long-term suppression of viral load with 2 nucleosides starting relatively early, has a proven track record. Now that several alternative nucleoside combinations are available, there is less risk that starting with nucleoside therapy will result in the exhaustion of options if drug resistance and a rise in plasma viremia is observed. I would recommend starting early with 3-drug combinations for subjects with a CD4+ cell count greater than 350/ $\mu$ L, for example, if three conditions are met:

1. Plasma HIV RNA level is greater than 30,000 copies/mL on at least two occasions.
2. The patient is committed to aggressive therapy and understands and accepts the importance of maintaining a high level of compliance with all three drugs.
3. The patient understands and accepts that use of a protease inhibitor with nucleosides may limit the effectiveness of alternative protease inhibitor therapy "down the road."

**Dr Vella:** The answer to this question needs to be investigated through controlled clinical trials. However, considering the resistance data, it is increasingly clear that, apart from tolerance and compliance issues, it may be desirable to start with regimens able to induce and maintain maximal viral suppression. Because resistant variants may exist before treatment and evolve under selective pressure, one can counteract viral resistance by using drugs where multiple mutations are required for resistance; using combination regimens based on mutually counteracting, drug-induced mutations, which may convert the unavoidable selection of mutant viruses into an at least partially favorable phenomenon; forcing the emergence of variants resulting in attenuated replication or decreased virulence; and finally, by maximizing the suppression of viral replication.

**19. Please define the range of CD4+ cell counts and plasma HIV RNA levels that would fall within the "moderate" disease category for which combination therapy with saquinavir was suggested?**

**Dr Volberding:** If the goal of therapy is to maintain complete or near complete HIV suppression, and if the pretreatment HIV RNA titer is very high (eg, above about 50,000 copies/mL), drugs with potent antiretroviral effect should be chosen. The current formulation of saquinavir has a somewhat limited effect, due to low bioavailability. If saquinavir is used in an initial regimen, the panel felt it should be aimed at those patients with lower plasma HIV RNA titers (eg, below about 50,000 copies/mL) who are in stable clinical condition. Newer saquinavir formulations with improved bioavailability or the simultaneous use of saquinavir with another drug (ie, ritonavir) to decrease saquinavir clearance may expand the role of saquinavir. In general, the first consideration in the choice of a protease inhibitor is antiretroviral potency and in that regard, despite the low toxicity of saquinavir, that more potent drugs should be used initially for patients with higher HIV RNA titers.

**20. If side effects are not an issue, are there any two nucleosides that should not be used together?**

**Dr Volberding:** In most cases, RT inhibitors should be used in combinations given the relatively limited potency of any single available agent. This recommendation may change when more potent RT inhibitors (eg, the nucleoside 1592U89) are introduced. Overlapping toxicity probably precludes the combined use of didanosine/zalcitabine or stavudine/zalcitabine. Very preliminary and in vitro data suggests caution with the combined use of zidovudine/stavudine, as they may compete for intracellular activation. Otherwise, most other two nucleoside combinations might be considered. Clearly, more laboratory and clinical data exist for some combinations than for others, but most seem comparable in antiretroviral activity.

**Dr Katzenstein:** There are two primary concerns that limit the combined use of nucleosides: toxic effects (as discussed above) and the concomitant resistance that may result from mutations in the polymerase gene. The issue of cross-resistance based on known polymerase gene mutations is much more complex. Theoretically, for example, the mutation at codon 184 (M  $\rightarrow$  V) that is rapidly induced by lamivudine also confers high-level resistance to didanosine and data from clinical studies evaluating the virologic efficacy of didanosine, after the administration of lamivudine are not yet available. Clinical data suggest that after long-term zidovudine treatment, there is little benefit to adding zalcitabine, even though zidovudine/zalcitabine is relatively effective initial combination therapy.

**21. What evidence supports the combination of lamivudine/stavudine? If HIV becomes resistant to lamivudine, what benefit does it**

## have in the combination compared with the combination of zidovudine/lamivudine?

**Dr Volberding:** The combination of stavudine/lamivudine is attractive because both drugs are well tolerated, administered bid, and can be taken regardless of food intake. Extensive safety data have been accumulated in clinical settings where the combination is frequently used by patients who can no longer tolerate zidovudine. Much less data exist, however, for the use of this combination as initial therapy, although studies are in progress. The use of zidovudine/lamivudine is supported, among other reasons, by the restoration in zidovudine sensitivity following the development of lamivudine resistance mutations. Whether this interaction is specific to zidovudine and will not occur with stavudine is yet uncertain. Also, it is not certain to what degree this interaction is responsible for the magnitude or durability of the antiretroviral effect seen with zidovudine/lamivudine. It may prove as effective to use stavudine/lamivudine but this is not currently supported by well-controlled studies.

**Dr Montaner:** Only pilot, uncontrolled data are available to date regarding the antiretroviral effect of stavudine/lamivudine. This combination is well tolerated and it can be expected to decrease plasma viral load by at least 1 log<sub>10</sub>. The durability of the response has not been established, but in my experience, it appears comparable to that of other 2-nucleoside regimens.

## 22. Why don't you say that at this time, due to lack of information and a desire to be cautious, that one begins with saquinavir because of possible lack of cross-resistance?

**Dr Volberding:** The issue of protease inhibitor resistance and cross-resistance is a thorny one. Most data are from in vitro studies of genotypic resistance. Data from clinical trials are still almost nonexistent. That said, while indinavir and ritonavir share many resistance mutations, saquinavir resistance is associated with fewer and different loci on the *pol* genome. It is not yet known whether this relatively different resistance profile is a function of the limited bioavailability of saquinavir. If this difference in profile persists with a more potent formulation, saquinavir may be recommended before other protease inhibitors. At this time, however, antiretroviral potency is the primary consideration in the choice of a protease inhibitor and, in its current formulation, saquinavir appears less potent than the other protease inhibitors.

**Dr Vella:** Whether the delay in the emergence of resistance is in fact a consequence of the high-level suppression of viral replication, or of the increased number or complexity of the mutations required to select for resistance—or of both mechanisms—is a question that remains to be

answered. Still, the possibility to delay resistance opens new scenarios for antiretroviral therapy, with the hope of translating long-term suppression of viral replication into a significant modification of the natural history of this disease.

## 23. How would you treat and monitor HIV-2 infected patients with a CD4+ count under 250/μL?

**Dr Volberding:** HIV-2 infection is rare in the US, mostly being seen in West African immigrants. HIV-2 causes AIDS but it tends to be a somewhat less aggressive virus than HIV-1. The nucleoside and protease inhibitors are active against HIV-2 as well as HIV-1, while the NNRTIs have no activity against HIV-2. It would seem advisable to approach HIV-2 clinically the same as HIV-1 following the plasma HIV RNA levels. It has not been established that the prognostic meaning of the plasma HIV RNA titer in HIV-2 infection is comparable to that in HIV-1 infection, but one can still use CD4+ cell counts in initiating and following response to therapy. Certainly, if the CD4+ cell count is severely depleted, combination antiretroviral therapy should be used, probably combining nucleosides with a protease inhibitor.

## ROLE OF OTHER DRUGS

### 24. Could you comment on the use of didanosine and hydroxyurea, and where this combination fits into your recommendations?

**Dr Volberding:** Laboratory studies have suggested that hydroxyurea may be useful in increasing the effective intracellular activity of didanosine, in particular. Clinical trial results have been somewhat mixed, although some benefit on laboratory endpoints has been reported. Hydroxyurea, even in the lower doses employed in these studies, has some toxicity and its bone marrow toxicity may blunt the CD4+ cell benefit usually associated with effective antiretroviral therapy. At this point, the use of hydroxyurea should be considered investigational only.

**Dr Montaner:** I agree with Dr Volberding. In our experience, hydroxyurea given at 500 mg po twice daily to patients already on chronic didanosine therapy led to substantial decreases in viral load. However, there were no changes in CD4+ counts. This dissociation of both markers is unusual and it remains to be fully explained. Toxicity was not a problem in our pilot study, however, this was a short-term trial involving a limited number of selected volunteers. At this time, therefore, we view this approach as worthy of further research but not yet ready for widespread clinical use.

**25. The *Guidelines* do not seem to consider acyclovir. While this is not a direct anti-HIV drug, if a patient had recurrent herpes, which seems to stimulate HIV replication, should this not be part of the anti-HIV drug therapy, as this drug could indirectly decrease (or slow) viral replication?**

**Dr Yeni:** For many years, it has been believed that a good scientific rationale existed for adding acyclovir to current antiretroviral therapy: prevention of a coincident HSV infection may inhibit HIV replication. A transient increase in plasma HIV RNA levels has been demonstrated during clinical HSV infection. However, conflicting results have been obtained from studies investigating the impact of acyclovir on clinical HIV disease, and no firm conclusions can be drawn. In addition, this debate has probably become less relevant now that potent anti-HIV drugs have become available. Therefore, in my opinion, routinely adding acyclovir to current antiretroviral treatment is not indicated.

**Dr Volberding:** The impact of co-incident infections in stimulating HIV replication has been of concern for years, and current viral load assays have increased this debate. HIV replication is probably increased nonspecifically by stimulation of immune response including that by vaccines and by coincident infections including HSV. Therefore, prevention of HSV reactivation may be of some value, even if acyclovir has no antiretroviral activity per se. HIV infection itself is not an indication for chronic acyclovir treatment, but many clinicians have a low threshold for recommending such therapy in persons with a history of HSV infection, given the low toxicity of acyclovir.

**Dr Katzenstein:** There is little evidence for or against the use of additional anti-herpes treatment (including acyclovir) as part of the treatment of HIV infection. The data in very advanced patients presented several years ago suggested that acyclovir and zidovudine were more effective than zidovudine alone. The contribution of acyclovir in this study is difficult to evaluate, since more potent antiretroviral regimens are now available. In patients with recurrent oral, anal, or genital HSV infection, the use of continuous acyclovir to suppress recurrences is an important adjunctive therapy. However, there are insufficient data to suggest that acyclovir has a role in anti-HIV treatment.

**26. What is the role of interferon alfa as a drug to use in a combination?**

**Dr Schooley:** Because of the relatively weak antiretroviral activity of interferon alfa in vivo, and because of the (primarily subjective) toxicity involved, there is little if any role for interferon alfa as an antiretroviral drug in combination therapy regimens.

**Dr Volberding:** Interferon alfa has some antiretroviral activity but is a cumbersome drug to use and is associated with side effects unacceptable to most patients. It should not be considered as a routine anti-HIV therapy.

**27. What is the potential of a foscarnet/zidovudine/indinavir combination?**

**Dr Volberding:** Foscarnet has anti-HIV activity but is a cumbersome, expensive, and toxic drug to use. It is not approved for HIV therapy per se and should only be used for such in the context of a controlled clinical trial. In the future, foscarnet or more likely derivatives of the parent drug may prove useful. At this time, however, foscarnet should only be used for the treatment of serious CMV infection or other herpes viruses resistant to less toxic drugs.

**Dr Richman:** Foscarnet has antiretroviral activity, and resistance patterns suggest that zidovudine and foscarnet would be a good antiretroviral combination. Unfortunately, both drugs have hematologic toxicity. Foscarnet is both quite toxic and difficult to administer. Thus, it can only be considered potentially useful for HIV if it is indicated for the treatment of a herpesvirus infection.

**28. Can you explain the rationale with which you will determine how to incorporate new, effective drugs into initial antiretroviral therapy regimen?**

**Dr Volberding:** The array of drugs and combinations of impressive antiretroviral potency is already substantial and will expand. It will be possible in many cases to design an initial treatment that can suppress plasma HIV RNA to undetectable levels, which is a reasonable goal of current therapy. It is not clear, however, whether the most potent therapy possible will be required initially in every patient. It may prove equally efficacious over the long term to adjust the potency of initial therapy to some degree to the estimated HIV burden and disease stage in an individual patient. Any hesitation to use maximally potent therapy initially is accentuated by the increased cost, toxicity, and compliance problems of certain combinations. As a result, newer drugs that are less expensive and easier to take may result in their relatively earlier usage. An important aspect of therapy selection, but one that is difficult to discuss concisely, concerns the design of long-term strategies that employ a large number of drugs in combinations. Here, it is assumed that many patients will not achieve complete HIV suppression and as a consequence will develop resistance to all of the drugs. Thus, it may be important to choose initial drugs and combinations that allow the broadest array of subsequent options. For example, it may prove wise to avoid the early use of a drug that causes cross-resistance to other drugs if a comparable, effective

alternative drug can be chosen. However, there are relatively little data on cross-resistance with which to make such a decision.

## **MONITORING, DOSING, AND OTHER CONSIDERATIONS**

### **29. Why is there no role for, or consideration of, monitoring drug levels and tailoring dosage regimens, when we hear of poor bioavailability, etc?**

**Dr Fischl:** Monitoring drug blood levels may prove useful in certain circumstances in the future. Several problems with bioavailability, as with the current formulation of saquinavir, will require an alternate formulation to achieve higher blood levels. The ultimate usefulness of monitoring drug blood levels remains to be seen.

### **30. In a patient with severe liver disease, what regimen would you recommend, since most nucleosides and protease inhibitors cause LFT elevation?**

**Dr Volberding:** While some LFT changes have been seen with many antiretroviral drugs, they are also common to HIV itself and associated disorders. Serious hepatotoxicity is rare with these drugs and they can be used safely in persons with pre-existing liver disease, although close monitoring should be initiated if liver function further declines. Of the protease inhibitors, indinavir has been most connected to concerns of liver disease, but the abnormality seen is a benign elevation of bilirubin.

**Dr Katzenstein:** Patients with severe liver disease are likely to experience an increase in hepatocellular enzyme levels (ALT and AST) in response to nucleosides. Fortunately, this hepatocellular toxicity can be rapidly reversed, once the drug is stopped. In initiating and monitoring antiretroviral treatment in patients with liver disease it is important to track both an antiretroviral response and hepatocellular enzymes levels. From the ACTG 175 trial, there was a significantly higher frequency of liver toxicity in the zidovudine-containing arms of the study, compared with didanosine alone. Thus, one suggestion may be the use of initial didanosine monotherapy in patients with severe liver disease. All three currently available protease inhibitors are metabolized by the liver and may have hepatic toxicity, but the risks of increased hepatotoxicity may be lower with saquinavir, where little hepatocellular enzyme elevation has been seen, even in studies using higher doses than those currently recommended.

### **31. Resistance does result from improper protease inhibitor dosing due to plasma levels, so, could you please emphasize the importance of proper dosing. I spoke to a patient with AIDS who was told by her MD to take ritonavir 800 mg qd. The current recommended dose is 600 mg bid.**

**Dr Volberding:** Resistance can develop with all antiretroviral drugs studied to date (although it has been difficult to document in some cases with available assays), and is especially likely and occurs particularly rapidly if the virus is allowed to replicate in the presence of the drug. Clearly, inadequate drug potency or drug levels would be inadvisable in this regard. The extremely rapid rate of HIV replication suggests that the antiretroviral effect should be maintained continuously. Thus, in addition to taking the correct drug dose, the patient must understand the need to take the medication on a rigorous schedule, and attend to the restrictions and requirements surrounding food intake. With drugs such as the first nucleosides, this attention to strict adherence was probably less crucial because complete suppression of replication was not possible, even in optimal settings. With current potent drugs, and combinations including the protease inhibitors or the NNRTIs, close attention to adherence is critical.

### **32. Is there a need for a loading dose?**

**Dr Volberding:** Loading doses of antiretroviral drugs are not usually needed. This possibility has been most carefully considered in the postexposure prophylaxis setting where a rapid onset of action and penetration of "sanctuary" sites might be important. However, loading doses are quite toxic and may limit the longer term adherence to treatment. In general, conventional doses should be used without loading.

### **33. If one had to choose therapy for a patient with less than 200 CD4+ cells/ $\mu$ L, would one pick the triple antiretroviral therapy or PCP prophylaxis, based on what we know today?**

**Dr Volberding:** A patient with a CD4+ cell count  $<200/\mu$ L is at risk for an increasingly wide and potentially fatal set of opportunistic diseases. Along with antiretroviral therapy, substantial progress continues in preventing certain infections with the prophylactic or preemptive use of antibiotics. As prophylaxis for *Pneumocystis carinii* pneumonia is straightforward and inexpensive, and as both it and antiretroviral therapy is of established clinical benefit, one should not choose between the two but should use both. It is difficult to imagine a situation where one would have to choose between trimethoprim/sulfamethoxazole and a protease inhibitor-containing antiretroviral combination.

**34. Your recommendations seem to focus on antiretroviral effect and resistance considerations. In practice, adverse drug reactions such as neuropathy limits choices—eliminating 3, possibly 4—RTIs.**

**Dr Carpenter:** This is a critically important issue, as one of the current realities in HIV treatment is that adverse drug reactions such as neuropathy considerably limit antiretroviral choices. Patients who are unable to take three or four of the current RTIs could take combination therapy with one nucleoside RTI and a nonnucleoside RTI or a protease inhibitor. Alternatively, two protease inhibitors (ritonavir and saquinavir) could be taken. We do not yet have adequate data on combinations including nonnucleoside RTIs to make definitive recommendations in this area.

**Dr Volberding:** Adherence certainly can be limited by side effects. In fact, from a patient's perspective, this is much more important than the selection of drug-resistant viral populations. Clearly, overlapping or pre-existing toxicity may preclude the use of specific drugs or drug combinations. An equally important consideration, particularly in those with more advanced disease, is the issue of drug-drug interactions. A patient may have antiretroviral options limited by the need to simultaneously use medications that affect each other's metabolism or side effects.

**35. What are the "proto drugs" on the horizon? How will we use them and what results can we expect?**

**Dr Volberding:** Numerous drugs are in clinical development and these will be brought into novel combinations with existing drugs quickly. The next drugs to gain approval in the US are probably delavirdine (an NNRTI; Pharmacia & Upjohn), 1592U89 (a nucleoside RTI; Glaxo Wellcome), nelfinavir (a protease inhibitor; Agouron), and 141 (a protease inhibitor; Glaxo Wellcome in the US/Vertex outside the US). The drug 1592U89 is of particular interest as it is a member of an "old" class of drugs, but its potency appears to be comparable to the protease agents and NNRTIs. This may permit the design of combinations that employ only a single nucleoside along with other drug classes. The protease inhibitor 141 is also of interest as it appears to achieve high CNS levels, unique, if true, compared with other members of this class of antiretrovirals. These drugs will probably be used in combinations according to the principle described above: potency, cost, toxicity, convenience, durability, OI response, and limitations on future treatment options.

**Dr Montaner:** Also, preliminary data were presented at the Vancouver conference regarding the possible role of lobucavir (a nucleoside RTI; Bristol-Myers Squibb) as an antiretroviral drug. This drug appears to have a broad-spec-

trum antiviral activity against herpesviruses, in particular, and a substantial anti-HIV effect.

**Dr Katzenstein:** In addition, new classes of drugs, based on their target, include drugs that inhibit HIV regulatory genes (eg, *tat* and *rev*), glycosidase inhibitors that target the envelope glycoprotein, drugs that target the integrase activity of HIV, and therapeutic approaches such as ribozymes and antisense RNA that use the sequence specificity of viral RNA and DNA as targets for intracellular destruction or inactivation. The discovery of additional receptors for HIV, the fusin protein and the chemokine receptors described this year, make them potential targets for therapeutic intervention since the identification of these ligands provides a basis for developing agents that block virus entry into cells.

These new drug therapies, as they progress through preclinical studies and into clinical trials will have to run the gauntlets tests of bioavailability, toxicity, drug/drug interactions, and effectiveness, each posing a unique set of challenges. We are now seeing the evolution of "proto strategies," the combination and sequencing of the existing classes of drugs. While we are still at an early stage in the refinement of these strategies, we can envision results that parallel some of the experience with other diseases that require multidrug therapy. In infectious diseases, the analogy is often tuberculosis; in oncology, it is lymphoma. These models suggest that prolonged and intense therapy with multiple drugs can induce a disease-free state, and that "maintenance" therapy in the case of hematologic malignancies can, in many cases, "consolidate" the gains in reduction in tumor burden to effect either a long-term remission or, in some cases, a cure. Any nontoxic therapy for HIV that can be shown to have an impact on virus replication, integration, or pathogenicity may have a place in these kinds of treatment strategies.

We can express cautious optimism that prolonged suppression of virus replication looks like the first step toward eradication and a cure. That being said, it is important to acknowledge that the flaws in current therapy, the capacity of the virus to mutate and develop resistance, the need for prolonged, multidrug therapy with rigid adherence to the drugs, and the unpredictability of the activity, bioavailability and tolerance of drugs and drug combinations will remain critical problems in the treatment of HIV infection, even as new drugs and classes of compounds are added.

**36. Please comment whether aggressive (3-drug) viral suppression may reduce horizontal transmission within the community.**

**Dr Fischl:** This will have to be addressed in future studies. However, as there are data to show that the risk of transmission is associated with inoculum size, significant suppression of virus in the circulation and genital secretions, should potentially decrease the risk for transmitting virus.

**37. Please comment on additive toxic effects on illegal drugs and best possible triple therapy HIV combination in an otherwise healthy candidate for this therapy. Consider HIV drug-free cases with drug addiction recurrences while on HIV therapy and possible clinical trials available.**

**Dr Fischl:** The major concern in this area would be hepatic toxicities and possible drug/drug interactions; to date the latter has not been a significant problem. The best triple-drug regimen is difficult to judge at this time; however, the most information is available for zidovudine/lamivudine/indinavir, which also appears to be well tolerated.

**38. What is the difference between clearance or decrease of viremia in acute infection compared with that following treatment?**

**Dr Richman:** The clearance rates of HIV virions during acute infection have not yet been measured as precisely as after chemotherapy. However, for a number of reasons this is likely to be short as well.

## **CHANGES IN PROPHYLAXIS REGIMENS**

**39. If you use combination therapy that includes protease inhibitors in patients with previous CD4+ counts of 200 cells/ $\mu$ L, and you are able to reduce their viral load and increase CD4+ count to greater than 200 cells/ $\mu$ L (stable), would you stop the prophylaxis?**

**Dr Schooley:** There is no question that the risk of opportunistic infections decreases as CD4+ counts rise in response to effective antiretroviral therapy. This is the basis for the clinical endpoint trials that have clearly shown that decreasing plasma HIV RNA levels and/or increasing CD4+ counts are related to reduced morbidity and mortality (ie, fewer opportunistic infections and a lower death rate). On the other hand, it is not clear that an individual whose CD4+ count rises from 150 to 250 cells/ $\mu$ L is at the same risk for opportunistic infections as someone with a CD4+ count of 350 cells/ $\mu$ L that is on the way down. Anecdotal experiences suggest that some individuals may experience recurrent opportunistic infections despite a significant rise in the CD4+ count following initiation of highly active antiretroviral therapy. Clinical trials are currently under development that seek to address this point and/or to identify laboratory or clinical features that allow more accurate assessment of risk-specific infections. Until such data are available, most clinicians will be reluctant to arbitrarily discontinue prophylaxis that

patients are tolerating, especially in the case of secondary prophylaxis, unless there are specific reasons to do so.

**Dr Carpenter:** Prophylaxis against PCP should probably continue in individuals whose CD4+ counts have risen to levels above 200 cells/ $\mu$ L while on combination therapy including protease inhibitors. It is not certain that the increased CD4+ count is accompanied by comparable restoration of other elements of the immune system.

**40. When the CD4+ count starts to rise above 300 to 400/ $\mu$ L, what is the recommendation for continuation of PCP prophylaxis?**

**Dr Schooley:** Given the low expense, high level of tolerance, and the potentially high morbidity and/or mortality of *Pneumocystis carinii* pneumonia (PCP), most would not discontinue PCP prophylaxis simply because CD4+ counts have risen above a certain number. However, clinical trials are required to address this point definitively.

**Dr Carpenter:** When the CD4+ count rises above 400 cells/ $\mu$ L in this setting, some clinicians would stop PCP prophylaxis, but there are no definitive data on which to base this decision.

**41. In a patient with a CD4+ count of 399 cells/ $\mu$ L and viral load below detectable levels, would you stop TB prophylaxis? (Patient is on ritonavir/lamivudine/stavudine).**

**Dr Schooley:** Within the constraints of drug interactions with ritonavir, it would be advisable to complete a course of therapy that had been initiated either for active disease or for a positive PPD.

**Dr Carpenter:** What is often called "TB prophylaxis" is actually treatment of latent tuberculosis infection based on a positive tuberculin skin test. An increasing CD4+ count and a viral load below detectable levels do not influence the need to treat latent tuberculosis in this setting.

**42. I am treating a patient with indinavir/zalcitabine who developed toxoplasmosis 12 months after seroconversion. Treatment was started after the onset of toxoplasmosis. Now her CD4+ count is less than 55 cells/ $\mu$ L. Would you consider stopping secondary prophylaxis?**

**Dr Fischl:** In the case of toxoplasma encephalitis, I would not stop secondary prophylaxis; therapy only kills the actively proliferating tachyzoite and not the dormant cysts. As long as this patient is immunocompromised from her HIV infection, she is at risk for relapse without secondary prophylaxis.