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International AIDS Society-USA

IMPROVING THE MANAGEMENT OF HIV DISEASE

SPECIAL ISSUE—

Answers to Questions Posed to the *Guidelines for Antiretroviral Therapy in 1996* Panel

VOLUME 4 SUPPLEMENT 1 NOVEMBER 1996

About The International AIDS Society-USA

The International AIDS Society-USA (IAS-USA) is a 501(c)(3) not-for-profit organization committed to improving the treatment, care, and quality of life of persons with HIV disease by providing balanced and relevant information to physicians. The IAS-USA programs are particularly intended to bridge clinical research and patient care. This publication is part of the ongoing efforts by the International AIDS Society-USA to provide information for physicians involved in HIV/AIDS care. Please contact us.

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ABOUT THIS ISSUE

On July 10, 1996, Antiretroviral Therapy for HIV Infection in 1996: Recommendations of an International Panel was published in the *Journal of the American Medical Association*. On that same day, the Panel convened at a special satellite symposium to the XI International Conference on AIDS in Vancouver, British Columbia, Canada. The goal of the symposium was to discuss the recommendations as published in the *Guidelines*.

The understanding of the pathogenesis of HIV and applications of treatment directed against HIV is undergoing rapid and continuous change. It was for this reason that the unique panel, which was sponsored by the International AIDS Society-USA (IAS-USA), was convened in January of this year. Each member of the Panel came to the *Guidelines* process with his or her personal views and approaches to treatment with antiretroviral drugs. Those views were presented, discussed, and used in the process to develop a reasonable and flexible set of recommendations for treatment that is hoped to form a basis on which antiretroviral treatment strategies can be made for individual pa-tients with HIV/AIDS. Clearly, much attention needs to be given to unanswered questions in the field. Hit very hard and very early? Make complete viral supression (ie, undetectable plasma HIV RNA levels) the goal of therapy for all patients? Initiate triple-drug therapy for HIV-infected pregnant women to reduce perinatal transmission risk? The conduct and completion of clinical trials that answer these and other important questions are eagerly awaited.

As noted in the *JAMA* article, the International Panel and the IAS-USA are committed to updating the recommendations as new data and information warrant. Even since publication of the *Guidelines*, new insights and therapeutic options have emerged. Included in these recent advances are preliminary clinical trial data and Food and Drug Administration (FDA) approval of nevirapine, the first available drug in the new class of nonnucleoside reverse transcriptase inhibitors. Delavirdine, another drug in this class, is available in the US under an expanded-access program as is a new protease inhibitor, nelfinavir, and these drugs may be approved by the FDA in the near future. Early results of clinical trials of triple-drug combinations, which include nucleoside, nonnucleoside, and protease inhibitor drugs, have been presented at scientific meetings. Some of these preliminary, short-term results show remarkable effects, particularly on plasma HIV RNA levels, the development of viral resistance, and in some instances, clinical outcome. Other investigations have further defined the dynamics of HIV in the host and the associations of plasma HIV RNA levels with disease progression and effects of antiretroviral treatment. Finally, the concept of viral "eradication" has evolved to a point that it can be evaluated in clinical trials.

The symposium started with introductory remarks from Dr Charles C. J. Carpenter, chair of the International *Guidelines* Panel; Dr Paul A. Volberding, chair of the IAS-USA Board of Directors and Panel member, and Dr Anthony S. Fauci, Director of the National Institute of Allergy and Infectious Diseases. The symposium faculty included all members of the Panel, including members of the Board of Directors of IAS-USA: Dr Margaret A. Fischl, also Co-Chair of the Panel; Dr Michael S. Saag; Dr Robert T. Schooley; and Dr Douglas D. Richman; as well as Panel members Dr Scott M. Hammer, Dr Martin S. Hirsch, Dr David A. Katzenstein, Dr Julio S. Montaner, Dr Melanie A. Thompson, Dr Stefano Vella, and Dr Patrick G. Yeni. A special (and refreshing!) break in the three-hour symposium was led by Dr Charles Steinberg.

More than 2000 people attended the presentation of the *Guidelines* at the satellite symposium in Vancouver and hundreds of questions about the *Guidelines* were submitted to the Panel. Time did not permit the discussion of all of the important issues raised by the audience. However, the questions were collected and consolidated, and they are addressed by the Panel in this special issue of *Improving the Management of HIV Disease*. As noted, the Panel will update the *Guidelines* as mature data permit. In the interim, we hope that this summary will provide further guidance and clarification of the recommendations of the International Panel. In large part, the responses to the questions presented here represent the views and opinions of the individual members of the Panel, rather than a panel consensus of the issues raised. The Panel will reconvene in November to discuss where updates in the *Guidelines* are needed, and this official consensus will be submitted for publication.

A Special Note of Thanks...

As many of you are aware, the symposium was temporarily, but violently, interrupted by a group of (purported) AIDS activists. The audience cheers of support for the Panel and outrage at the senseless disruption, combined with the integrity and commitment of each member of the Panel, allowed the symposium to continue. I wish to thank the audience members for their support. Please know that all of your written comments of admiration, gratitude, and genuine concern for the safety and well-being of the Panel have been shared with each of its members, and I share their thanks with you.

With you, and on behalf of the many people who have written and called to relay their appreciation to the Panel, the staff of IAS-USA wishes to convey their most sincere words of admiration for the members of the Panel. We, the staff, have had the privilege to watch each of you volunteer your time, energy, and talents—in the face of your many other important and pressing contributions to the field—toward working to develop a set of recommendations for care in an exciting and evolving, but complex and ever controversial, field. And to the special group of people who comprise the volunteer Board of Directors of the IAS-USA: your vision, energies, and great spirit are the backbone of the organization. It is the continued devotion of all of you that inspires us at IAS-USA to devote our energies to working with you in furthering our mission.

A special note of thanks to all of you!

Donna Jacobsen
Executive Director
International AIDS Society-USA

PRIMARY (ACUTE) INFECTION

CHARACTERISTICS AND DIAGNOSIS OF PRIMARY INFECTION

1. To diagnose primary infection, expensive laboratory tests will probably need to be ordered. Given the expense, which test should we order? p24 antigen? Plasma HIV RNA?

Dr Richman: Within several days of infection, all patients will probably have a positive test for plasma HIV RNA for life in the absence of potent chemotherapy. A plasma HIV RNA test (either by RT PCR or the second generation branched DNA [bDNA] assay) is thus almost completely sensitive and specific. The p24 antigen assay is equally specific and less expensive. It will be positive during primary infection most of the time, but not always. Thus, a plasma HIV RNA test would be the quickest and simplest approach to diagnose primary infection. A less expensive approach may be to get a p24 assay; a positive result is diagnostic, but a negative result would require a plasma HIV RNA assay for confirmation.

2. In acute infection, does dissemination of HIV-1 seed out to sites other than lymph nodes?

Dr Richman: During primary infection, HIV replication is established in the lymphoid tissue, the central nervous system, and the genital tract (where high levels of virus shedding and transmission can occur).

3. When you consider latently infected CD4+ cells during primary infection, how can eradication be even theoretically possible using currently known therapeutics?

Dr Richman: If cells become latently infected during primary infection, then eradication is only theoretically possible if the latent cells have a finite lifespan (in contrast to ganglionic neuronal cells with herpes simplex virus or varicella-zoster virus infection) and if chemotherapeutic suppression is maintained until the latently infected cells expire and are replaced. Whether these theoretical possibilities prove to be the case requires systematic investigation, which is now under way.

INITIATING TREATMENT FOR PRIMARY INFECTION

4. Would you treat an at-risk patient (eg, a young gay man) presenting with compatible clinical syndrome (eg, aseptic meningitis) with anti-HIV therapy before test results are available? Most practice settings have more than 2-week delays for p24 or HIV RNA tests.

Dr Saag: Ideally, individuals with acute infection should be treated as early in the clinical course as possible in order to achieve maximum clinical benefit. The difficulty is not so much determining when to treat, but whether to treat at all. The decision to treat a probable but not confirmed case involves a difficult risk/cost analysis, which would sway one to treat only if one's confidence were fairly high. Because the acute HIV syndrome is not specific with regard to clinical presentation, presumptive therapy may often be directed at non-HIV symptoms. In the situation described, I would favor treatment initiation, pending the results of virologic testing.

The decision to treat early is based on pathophysiologic data and, to a large degree, clinical intuition, to protect uninfected cells from becoming infected at a time when the virus is spreading rapidly throughout the body (eg, brain, testes, gut). Through aggressive antiretroviral therapy, it is theoretically possible to prevent or minimize spread of the virus to these tissues. Moreover, at the time of initial infection, a single genotype (strain) of the virus predominates. Within 2 to 4 weeks after initial infection, that viral strain has begun to generate genetic variants, which provide an opportunity for the virus to escape selective pressure from drug therapy. By treating very early and aggressively, viral replication can be minimized, thereby minimizing the likelihood of development of resistant viral virions over time.

REGIMENS FOR PRIMARY INFECTION

5. What do you think of using NNRTIs early on as an additional strategy?

Dr Saag: The NNRTIs are especially attractive potential drugs for primary infection because they do not require the cellular processing to become active antiretrovirals (as is required for nucleosides, for example, which require cellular phosphorylation). In addition, the NNRTIs achieve high serum and cellular concentrations very early after the

initial dosing and are therefore especially attractive for primary infection as well as acute exposure (eg, after a needle stick injury in health care workers). The use of NNRTIs in combination with protease inhibitors should await results of studies assessing the safety and pharmacologic interactions of such combinations.

Dr Montaner: Although it is premature to characterize the best time to use NNRTIs, the nevirapine experience provides important clues in this regard. I generally favor the inclusion of NNRTIs in a 3-drug regimen when at least two (if not all three) of the drugs are new to the given patient. This approach applies regardless of disease stage. Until further data are available I would tend to favor the inclusion of NNRTIs within combination therapy regimens aimed to fully suppress viral replication. NNRTIs are relatively "fragile" compounds in that high levels of resistance require only one mutation, and for this reason full suppression of viral replication is necessary to protect their antiretroviral effect.

6. What do you think about coadjuvant use of immunotherapy during primary infection?

Dr Saag: The term immunotherapy represents a vast array of possible treatments ranging from immune stimulation (eg, interleukin-2) to immune suppression (eg, prednisone or cyclosporin). In view of our very limited knowledge of the nature of the immune response during acute infection, it is probably not wise to introduce immunotherapy of any sort during this period. The rationale behind the use of antiretroviral therapy is based in large degree on a fairly deep understanding of HIV pathogenesis and its relationship to viral replication. We do not have a comparable understanding of the immune response to HIV and interventions are as likely to do harm to a patient as good.

How Long Should Treatment for Primary Infection Continue

7. How would you manage a patient with acute infection if measurement of viral load is not available to you? After deciding to initiate therapy for primary infection, can one ever stop administering the drug?

Dr Saag: In most instances, the goal of treatment is to minimize the immune system destruction, and to maximize viral suppression, thereby minimizing the likelihood of development of drug resistant isolates over time. In such instances, therapy might best continue throughout the entire course of infection. If the rationale to initiate treatment was to completely eradicate HIV from an individual, then it would make sense to stop therapy at such time that the clinician believes that the goal of eradication has been achieved. At present, however, it remains uncertain whether such a result can be achieved. It is speculated that it will take at least 2 to 4 years of chronic, aggressive suppressive therapy, to achieve this objective, if at all. Moreover, viral load measurements would be necessary in this strategy in order to demonstrate complete suppression (undetectable viral levels) for an extended period of time. In my opinion, in most instances, chronic viral suppression should be continued throughout the course of infection regardless of whether viral load measurements are available. A practical approach, if suppression is attained, would be to continue therapy and closely follow new developments in this rapidly changing field.

Other Issues

8. Why not use "virograms" to determine the resistance mutations of the recently-infected person?

Dr Katzenstein: Practical assays of reasonable expense to assess drug susceptibility or resistance mutations are not yet available. In most situations, it is currently easier and faster, and, perhaps, more relevant to evaluate the plasma HIV RNA response of the patient than to test his or her virus isolate for susceptibility or genetic sequence.

There are a number of in vitro techniques that are being developed to assess drug susceptibility. The use of the term "virograms" suggests use of viral sensitivity testing in which phenotypic susceptibility (analogous to the susceptibility testing for bacteria in the microbiology lab) is determined on an isolate or a recombinant virus derived from the patient. This is being developed, and is available as a research tool from a few laboratories. In addition, genetic sequencing from plasma HIV RNA is being explored as a method to detect resistant genotypes in the circulating virus population. These are both important epidemiologic tools. For example, they have been used to describe an increasing frequency of zidovudine-resistance mutations among isolates from seroconverters. However, in practice the value of this type of testing may be greatest when we have a clear understanding of the meaning of the results and have additional drug strategies that can be guided by such an approach. The presence of circulating virus, which is necessary for testing, already provides evidence that current drugs have failed.

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/μL (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 antiretroviral combination therapy against which we should judge future drugs or drug combinations in patients with CD4+ cell counts >350-500/μL? 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/μL 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 antiretroviral 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/μL, 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 → 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 $\log_{10}$. 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 been 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/μL, 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/μL 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-spectrum 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 impredictability 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/µL, and you are able to reduce their viral load and increase CD4+ count to greater than 200 cells/ µL (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/µL is at the same risk for opportunistic infections as someone with a CD4+ count of 350 cells/µL 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/µL 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/µL, 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/µL 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/µL 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/µL. 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.

CHANGING (CONTINUING) THERAPY

WHEN TO CHANGE

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

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

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

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

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

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

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

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

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

WHAT TO CHANGE TO: GENERAL

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

What to Change to: Role of NNRTIs

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

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

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

What to Change to: Intolerance

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

POSTEXPOSURE PROPHYLAXIS

WHO SHOULD BE TREATED

79. Does the Panel's definition of exposure include high-risk sexual activities, not just occupational exposure? What are the Panel's recommendations for prophylactic antiretroviral therapy for high-risk sexual exposures?

Dr Fischl: The current postexposure recommendations relate only to occupational exposure. No formal recommendations were made regarding high-risk sexual activities as more definitive data are needed about risks and interventions. However, many members of the Panel regard high-risk sexual exposures as analogous to high-risk occupational exposures and would follow similar guidelines in recommending postexposure prophylaxis.

80. Should therapy be recommended for a patient who may have been exposed to HIV during a surgical procedure in which the surgeon suffered a previous percutaneous exposure (unrecognized or not)? Should testing of the surgeon be mandatory in such a case?

Dr Fischl: Current information would indicate that there is an extremely low risk for patient acquisition of HIV infection from a health care worker and no guidelines for mandatory HIV-testing of health care workers have been made. However, if one surgeon in this case is known to be HIV infected, postexposure prophylaxis would be recommended for the patient.

81. What are the recommendations for prophylaxis for accidental needle injuries in subjects who are not in an identified high-risk setting (eg, a child with an accidental needle puncture)?

Dr Fischl: One would anticipate that the risk for HIV infection would be low in such instances; however, if there is any suspicion that there was a high-risk exposure to HIV-infected blood then the current *Guidelines* should be followed.

82. Should prophylaxis be recommended for mucosal exposure to HIV? For surface skin exposure?

Dr Fischl: For mucosal membrane exposure, the CDC guidelines suggest offering antiretroviral therapy for exposures to visible blood or other infectious fluids. Skin exposure recommendations have been restricted to increased risk that involves an exposure to a higher titer of HIV, prolonged skin contact, or an extensive area in which the skin integrity is visibly compromised. For increased-risk skin exposure, the CDC guidelines suggest offering antiretroviral therapy for exposures to blood and fluid containing visible blood or other infectious fluids.

83. Is prophylaxis recommended in all accidental injuries (even from healthy sources?)

Dr Fischl: Prophylaxis is recommended for high- and increased-risk exposures from an infected source patient. If the HIV status of the source patient is not known, a decision about prophylaxis should consider the exposure risk and likelihood of HIV infection in the source patient. Once initiated, prophylaxis can always be stopped if subsequent information indicates minimal or no risk of HIV exposure.

THE USE OF LABORATORY MARKERS IN POSTEXPOSURE PROPHYLAXIS

84. Are p24 antigen or PCR tests useful in deciding whether to recommend postexposure prophylaxis? Can plasma HIV RNA testing at 2 to 3 weeks after accidental exposure help to rule out the possibility of infection sufficiently enough to defer the 6 to 12 months antibody testing?

Dr Hirsch: Blood should be drawn acutely (ie, at baseline) and then periodically for at least 6 months postexposure (eg, at 6 weeks, 12 weeks, and 6 months) for conventional anti-HIV testing. The place of plasma HIV RNA or p24 antigen testing for monitoring whether infection has occurred or the need to continue prophylaxis in this setting have not yet been established. At present, it cannot be concluded that an undetectable plasma HIV RNA level or a negative p24 antigen test shortly after exposure rules out the possibility of infection sufficiently enough to defer the 6-month antibody testing.

What Regimens Should be Used for Postexposure Prophylaxis

85. Postexposure prophylaxis is so rare, and data on zidovudine have not been conclusive. Isn't it too drastic to go for 3 drugs?

Dr Hirsch: The most convincing evidence for zidovudine postexposure prophylaxis is the case-control study published by the CDC in which zidovudine use reduced seroconversion after significant occupational exposure by approximately 80% during the period between 1988 and 1994. Given the greater likelihood of zidovudine resistance currently and the benefits shown for 3-drug combination regimens in other settings of established HIV infection, the recommendations for their use in the most significant exposures are considered appropriate at this time.

Dr Montaner: I would add that postexposure prophylaxis is no longer a rare event. At our institution we have noticed a substantial increase in the demand for intervention after the publication of the CDC study on this issue.

86. What is the role of nevirapine monotherapy for postexposure prophylaxis?

Dr Hirsch: The role of nevirapine monotherapy in postexposure prophylaxis has not been established. However, nevirapine or delavirdine theoretically may be useful drugs for short-term prophylaxis when used in combination with other drugs for high-risk exposures, particularly if the source patient has not received these NNRTIs.

Dr Montaner: NNRTIs are attractive drugs for use in postexposure prophylaxis. However, until further data are available they should be regarded as experimental in this setting. Under some specific circumstances I would be prepared to use them as part of a combination therapy scheme.

87. Does it matter what the viral load of the source patient is in deciding future therapy?

Dr Hirsch: The viral load in the source patient is probably very important in determining risk, but this information is rarely available at the time occupational exposures occur. The clinical state of the source patient and his/her treatment history are more frequently known. It is likely that as viral load measurements become more frequent, this information will become very useful in assessing risk.

How Long Should Therapy Continue and When Should It be Started

88. Should the period of the proposed treatment for postexposure prophylaxis be shortened to 2 weeks if the regimen includes a protease inhibitor? Also, why stop at 4 to 6 weeks?

Dr Hirsch: The optimal duration for postexposure prophylaxis is unknown. Based on the biology of the virus, shortened durations of potent 3-drug regimens are reasonable. However, it is unclear whether this should be 2, 3, or 4 weeks, or some other duration. Durations beyond 6 weeks are not recommended because there is no evidence that longer treatment is beneficial, and the toxicity and expense are certainly greater with prolonged therapy.

Dr Fischl: As stated, the optimal duration of prophylaxis is not known. Data from the CDC case-control study suggested that 4 weeks of zidovudine were protective. Therefore, the current recommendations are to treat for 4 to 6 weeks, if tolerated. Whether a more potent regimen can be given for a shorter duration is unknown.

89. What is the maximum time delay that would be acceptable before initiating prophylactic treatment in a high-risk postexposure situation?

Dr Fischl: Ideally, therapy should be started within 1 to 3 hours and certainly within at least 24 to 36 hours. The interval after which prophylaxis is no longer beneficial in humans is unknown. Initiating prophylaxis after a longer period of time, however, should still be considered for a high-risk exposure. Although HIV infection will likely not be prevented, the early treatment of HIV infection may be beneficial, and studies are being conducted to evaluate triple-drug regimens that include protease inhibitors for the treatment of acute seroconversion and early HIV infection.

Dr Hirsch: As noted, we cannot determine today what is the maximum acceptable delay. Data from animal and human studies indicate that the rule to follow should be "the sooner the better," preferably within a few hours.

90. An RN had massive exposure of blood to open blisters on her hands during cardiac arrest of an AIDS patient. She has been on

zidovudine for 3 weeks and then consults you. What do you add now to the regimen?

Dr Hirsch: Given the nature of the exposure and the length of time that has elapsed since the presumed contact, I would not add a second drug to the regimen at this time, unless there is strong evidence that the source patient was likely to have zidovudine-resistant virus.

Dr Fischl: If the exposure was from a patient known to have drug resistance or had been treated with zidovudine for a prolonged period of time, an adjustment in the regimen might be made. Initiating a change in prophylaxis should still be considered because of the high-risk exposure. Although HIV infection may not be prevented, the early treatment of HIV infection may be beneficial, and studies are being conducted to evaluate triple-drug regimens that include protease inhibitors for the treatment of acute seroconversion and early HIV infection. The effectiveness of changing prophylaxis in such a setting, however, is still unknown.

Other Issues

91. HIV infection acquired through occupational exposure may imply some responsibility on the part of the health care facility—ie, for disability or for other compensation. This implies that periodic HIV testing of health care workers (HCWs) may be necessary to ensure documentation of occupationally acquired infections. What is your position on mandatory testing of HCWs in general?

Dr Fischl: Occupational exposure does not require mandatory HIV testing. HIV testing can be done at the time of the exposure and should be negative if the health care worker was seronegative at the time of the exposure. A positive HIV antibody test after seroconversion would be expected after 2 to 6 weeks.

Dr Richman: Routine (every 6 to 12 months) blood drawing and serum storage with voluntary testing for HIV should be standard practice in laboratories working with HIV or other biohazardous materials.

92. Please do not forget to emphasize rapid and complete local cleansing of injured/exposed areas.

Dr Fischl: Cleaning of a local injury or exposure with soap and water is always a good hygienic practice and should be done.

93. Would immediate surgical resection of an involved hematoma be recommended in a high-risk needle impaled, for example, in someone's muscle?

Dr Fischl: Virus would likely be rapidly disseminated through the blood stream and resection of the hematoma would not necessarily decrease the risk of seroconversion.

94. Instead of giving a cocktail of drugs, should we reserve one drug for postexposure prophylaxis that will never be given to patients (so there will be no resistance issue)?

Dr Fischl: It would be difficult to withhold therapy from patients in light of the current treatment regimens available. In addition, monotherapy is likely to be less effective and combination therapies are likely to be required.

PREVENTION OF PERINATAL TRANSMISSION

ANTIRETROVIRAL REGIMENS FOR HIV-INFECTED PREGNANT WOMEN

95. Will aggressive therapy of the pregnant woman resolve the issue of vertical transmission?

Dr Schooley: The mechanism(s) by which HIV-1 transmission is prevented by zidovudine monotherapy has not yet been delineated. Although the likelihood of transmission decreases as the maternal plasma HIV RNA level declines, no level has yet been identified below which transmission does not occur. It has not been demonstrated that the effect of zidovudine on decreasing plasma HIV-1 RNA levels is responsible for prevention of transmission. Thus, although it is possible that it will be demonstrated that lowering viral load in the mother does play a role in prevention of vertical transmission, it is also possible that the most important issue will be intensification of the regimen delivered to the baby.

Dr Thompson: In studies to date, transmission has occurred even with very low levels of HIV RNA in some patients. It is not certain therefore that more complete viral suppression will result in the absence of vertical transmission. Maternal and obstetric factors may contribute, and the importance of treating the neonate should be stressed. From clinical trials of nonpregnant patients we know that suppression of plasma viral RNA does not fully account for the treatment effect. However, if potent combinations are capable of more completely turning off viral reproduction, additional benefit will likely be seen.

96. What studies are being conducted in pregnant women, both to enhance their health and to prevent perinatal transmission by using combination therapy and decreasing viral load, especially at delivery?

Dr Schooley: Second-generation studies using combinations of antiretroviral drugs are in the pilot phase. Studies are also under way that seek to identify whether antiretroviral treatment of the mother or the child, or both, are important in preventing transmission. Finally, there is increasing interest in "eradication" studies in infected infants based on pilot data generated with triple-drug regimens.

Dr Thompson: Safety studies are under way using stavudine monotherapy, combination lamivudine/zidovudine, and combination nevirapine/zidovudine. A large combination study of zidovudine/lamivudine has been initiated and many have chosen to use this combination because of reasonable safety experience to date. The most interesting data on combination therapy come from a trial using nevirapine in combination with zidovudine just prior to delivery, but even these data are insufficient to uniformly recommend this regimen for all pregnant women. The Panel will be watching these data closely as they mature. As of this publication, no studies have been initiated using protease inhibitors in pregnancy and there are only rare cases of pregnant patients being treated in the expanded access programs for indinavir, ritonavir, and saquinavir. In all cases, clinical trials of protease inhibitors have excluded pregnant women or mandated discontinuation of the drugs if pregnancy occurred. There is particular concern about indinavir in this setting because of the known complication of hyperbilirubinemia with this drug. Animal toxicology studies found an increased incidence of ventricular septal defect (VSD) in animals treated with delavirdine and to date only a few pregnant women have been treated with the drug. In one pregnancy that ended in premature birth, the neonate had a VSD that closed within four weeks and was felt to be typical of prematurity rather than an effect of delavirdine treatment. Numerous studies are being planned using protease inhibitors or NNRTIs in third-trimester pregnancy and in neonates. Development of a formulation appropriate for neonates is a challenge in the case of some of these drugs.

97. Why is the committee being so timid regarding vertical transmission and combination therapy given the good preliminary data?

Dr Schooley: The Panel has sought to make recommendations that represent a reasonable balance between data that have emerged from clinical trials and inferences that can be made from the rapidly developing understanding of HIV-1 pathogenesis. In rapidly moving fields such as this, one should expect that recommendations will evolve as data emerge and that there will be a number of opinions about specific issues that are in transition. In the case of perinatal transmission, we are hampered by the fact that only a single clinical trial, which was planned at the beginning of the decade and which used only a single drug that we now know to be a relatively weak antiretroviral drug, has been completed. It is likely, nonetheless, that several members of the Panel might be on the more aggressive end of the spectrum (as it appears the questioner might be).

Dr Thompson: As mentioned above, there are actually scant preliminary data regarding the use of combinations

in pregnancy. There have been no completed studies of combination therapy with enough patients to demonstrate effectiveness. Because of the unique safety issues associated with treatment during pregnancy, it is important to have a substantial safety database from clinical trials before recommending use of a particular combination for all women. Broad guidelines with public health implications must be somewhat more conservative than one might wish, particularly when not even scant safety data exist. The unique feature of the IAS-USA *Guidelines* is that they are dynamic and will be updated regularly to accommodate rapidly emerging new data.

98. The life and well-being of the mother is the single most important factor for the health and well-being of the child. What data do you have to recommend that treating a pregnant mother for her own infection is secondary to that of the child?

Dr Schooley: The Panel does not believe that treating the mother should be secondary to that of the child. Although data have not been unequivocally established that antiretroviral therapy in the mother improves fetal well-being, in other settings the health of the mother and that of the child are closely related.

Dr Thompson: The Panel's recommendation to use zidovudine alone in pregnancy is not based on the premise that the mother's treatment is less important than the child's. Yet we cannot ignore that significant birth defects can occur when drugs are given during pregnancy and it would be irresponsible to recommend the use of drugs for which there are no safety data. Because pregnancy is a time-limited condition, it is expected that more aggressive treatment, for example, with nucleoside/protease inhibitor combinations, may be appropriate for many patients following delivery. There is no evidence to suggest that deferring treatment with protease inhibitors during pregnancy is detrimental to the patient's long-term course. At present, the optimal time for initiating treatment with protease inhibitors is uncertain.

99. What changes in therapy should be made for an HIV-infected woman who is considering becoming pregnant?

Dr Thompson: There are no specific recommendations for women who are contemplating pregnancy, although it should be recognized that there are no data at all to guide us on giving protease inhibitors in any stage of pregnancy, particularly the first trimester. Nevirapine has only been given in the last trimester, and most safety studies involve only the last trimester. A concern that cannot be fully addressed at this time is whether protease inhibitors should be stopped in women who become pregnant. Although there are no safety data to support continuing therapy, the risk of developing viral resistance must be considered. In the absence of safety data, a conservative approach may be to delay the initiation of protease inhibitors in a woman who is actively trying to conceive. The safety database on these drugs will be expanding rapidly within the next year.

100. For most women who present for prenatal care, the time of their seroconversion is unknown. Should we provide combination therapy with two drugs only if she is zidovudine-naive, or should we be more aggressive if her CD4+ cell count is less than 350/µL? What is the alternative to zidovudine?

Dr Schooley: Opinions in this area are changing rapidly. Although the zidovudine monotherapy recommendation for previously untreated women is well-founded in the ACTG 076 data, more aggressive regimens are being introduced outside the clinical trials setting. Several nucleoside combinations could be considered, and caution must be exercised regarding these drugs and with drugs that have a significant effect on bilirubin excretion (such as indinavir) in the perinatal period.

Dr Thompson: Many would consider zidovudine/lamivudine during pregnancy in the setting of more advanced disease and in a patient who is zidovudine-experienced. This is the nucleoside combination with the largest body of safety data. A short course of nevirapine prior to delivery may also be considered in light of recent clinical trial data.

101. In mothers with CD4+ counts >500 cells/µL, do you continue antiretroviral therapy postpartum? What are the risks of HIV-resistant strains developing after therapy is stopped?

Dr Thompson: In most cases I would not discontinue antiretroviral therapy in the mother following pregnancy, but would intensify it since zidovudine monotherapy is no longer appropriate long-term therapy. Until we are able to achieve viral eradication, therapy for HIV should be considered a lifelong endeavor. Although we do not currently have data to confirm that treatment at higher CD4+ cell counts confers long-term benefit, my treatment approach is rather aggressive based on the theory that early disease is the optimal time to initiate potent treatments to achieve the most complete viral suppression. There is little doubt that therapy should be continued with more than one drug for a woman who is symptomatic despite a high CD4+ count. Likewise, if viral load either before or following pregnancy was detectable, I would continue and optimize treatment.

The issue is less clear for a woman with a high CD4+ count, an undetectable viral load, and no symptoms. If viral load before and after pregnancy was undetectable some might consider discontinuing. However, if treatment is discontinued, I would monitor viral load 2 to 4 weeks after discontinuation and restart treatment with a more aggressive regimen if HIV RNA is measurable.

Dr Richman: The treatment for adults with >500 CD4+ cells/μL depends on the deliberations of patient and physician, as discussed in the *Guidelines*. The plasma HIV RNA level should help in this decision. Resistance should only develop in the presence of the selective pressure of drug therapy, not after discontinuation.

When Should Treatment for the Neonate Begin

102. Up to what age should a neonate be treated for 6 weeks with zidovudine? For example, the mother is found to be HIV-infected when the baby is 1 week of age, should you still treat the baby?

Dr Schooley: There are no data that specifically address this point. If it is true, as some suspect, that the major impact of perinatal antiretroviral chemotherapy is to essentially preemptively treat primary infection, a week's delay might greatly decrease the likelihood of prevention of transmission. Nonetheless, in that data are not available, it would be an error to impose a specific cutoff of hours or days past delivery after which one would not treat a child in this setting. At the very least, if infection is not prevented, emerging data in adults that suggest a benefit of treating primary infection, by extension, raise the possibility that the child might benefit even if transmission is not prevented.

Dr Thompson: Treatment of the neonate is important even if it is not begun prenatally or immediately following birth. The child should be treated regardless of whether the mother was treated and regardless of the interval elapsed since birth. However, it is reasonable to suspect that zidovudine alone will be less effective in preventing primary infection the longer treatment is delayed. If treatment cannot be initiated early, more aggressive therapy such as combination zidovudine/lamivudine could be considered.

Regimens for Neonates

103. Which protease inhibitor would you recommend for the treatment of HIV-infected neonates? Would you assess the mutation pattern in mothers before treating the infant?

Dr Thompson: At present, no protease inhibitor can truly be recommended since there are no safety data on any of them. However, there would be safety concerns about using indinavir because of the known hyperbilirubinemia with this compound. Genotypic analysis is not routinely available to most clinicians and the clinical implications of the results are not yet understood. It is premature to routinely use genotypic analysis to guide therapy. However, in a woman who is likely to carry zidovudine-resistant virus, treatment with combination zidovudine/lamivudine or a nevirapine-containing regimen may be considered.

Dr Richman: Until safety and pharmacokinetic studies with protease inhibitors are completed in neonates, the use of these drugs cannot be recommended.

104. Is therapy recommended for all children born to HIV-infected mothers? Instead, should the viral load of neonates be measured, and, if the infant is infected, should the infant be treated? There is no point in offering treatment to a child who is not infected, as there is a 20% to 30% probability of infection in untreated mothers and a 2% to 8% probability of infection in treated mothers.

Dr Thompson: Therapy is recommended for all children born to HIV-infected mothers. Since viral load cannot be assessed instantaneously at birth, it appears safer to treat the child first. There is no evidence from ACTG 076 that treatment in the neonatal period is harmful to the child, and early therapy has the best chance of preventing transmission. It should be noted that neonates were also treated in ACTG 076 and that neonatal treatment may have contributed to the lowering of the transmission rate to 8% seen in that study.

Breast-Feeding Issues

105. Does the Panel's recommendation that HIV-infected mothers not breast-feed conflict with the World Health Organization's recommendation for women in developing countries?

Dr Thompson: The Panel's recommendation is to avoid breast-feeding "where local conditions permit." This recommendation seeks to recognize the very complicated issues surrounding breast-feeding and the use of bottled nutrition in developing countries. The Panel supports the World Health Organization (WHO) recommendation for

breast-feeding in general, but not in the case of HIV infection if there are other viable options for neonatal nutrition.

106. Can breast milk be treated with drugs to eradicate the virus in the milk itself, thus making it safe for the baby?

Dr Thompson: There are no data regarding treatment of milk to eradicate virus.

107. When both mother and baby are taking zidovudine and breast-feeding continues, should we worry about toxic zidovudine levels in the neonate?

Dr Thompson: As noted, breast-feeding should be avoided, when possible. Although zidovudine can be detected in the breast-milk in women who were taking the drug, the risk for additional toxicity in the neonate appears to be low.

Other Issues

108. Since zidovudine has been shown to reduce the rate of vertical transmission, is it unethical to include a placebo arm in the UNAIDS clinical trial that will be conducted in Africa?

Dr Richman: Ethical decisions are often relative. The circumstances in the United States and western Europe are such that it would be inappropriate to conduct a placebo controlled study. In many African countries the introduction of chemotherapuetic prophylaxis for maternal-fetal transmission can be supported only if modifications of the relatively complex and expensive ACTG 076 are sufficiently effective. Consequently, the UNAIDS study of zidovudine/lamivudine includes a number of potentially simplified, shorter regimens and a placebo control to assess efficacy and cost-benefit in a different socioeconomic setting. An expert advisory panel consisting primarily of representatives from developing countries concurred that, in this situation, a placebo control was not only acceptable, but necessary.

Dr Thompson: It should be noted that the standard of care in the communities involved in this study is still "no treatment" because of the complexity and expense of the ACTG 076 regimen.

109. Do you recommend abortion for all HIV-positive pregnant women?

Dr Richman: No.

Dr Thompson: No.

110. Since an 8% transmission risk is still very high, the mother is unlikely to be able to raise the child to adulthood, and the long-term risk of antiretroviral exposure is uncertain, even if the baby is not known to be infected, should infected women be strongly encouraged to have an abortion?

Dr Richman: Decisions about abortion are the ultimate responsibility of the mother. In the ideal situation, this decision involves deliberation with the guidance of the health care provider and family members taking into consideration all the important and relevant issues including personal, medical, economic, and religious ones, among others. The risk of infection to the newborn and the existence of a chronic medical condition in the mother, of course, should be included in the complex decision-making process.

Dr Thompson: While abortion is a viable option for many women with HIV, it should not be presumed that it is the preferred option, and the provider's biases should not be visited upon the patient. Abortion should be discussed in the context of information about the risk of transmission, the importance of antiretroviral treatment during pregnancy, the patient's support system, and the patient's overall wishes for children and means to support them.

111. In view of the dramatic decrease possible in vertical transmission to neonates given zidovudine, should prenatal testing of pregnant women be mandatory?

Dr Richman: Ideally, all pregnant women should be tested for medical conditions that could impact the newborn, including the presence of hepatitis B virus (HBV) and HIV infection. The potential negative consequences of mandatory testing probably make organized educational efforts and voluntary consent to prenatal testing a more effective policy.

Dr Thompson: Voluntary testing is extremely well received (98% or better in some studies). Mandatory testing cannot do much better and may result in avoidance of prenatal care and lack of trust in the health care provider at a time when the establishment of trust is critical for the health of the pregnancy.

ROLE OF PLASMA HIV RNA TESTS

112. In view of the lack of widespread accessibility and costs of HIV RNA testing, would you recommend routine determinations for asymptomatic, stable patients on initial therapy who have stable CD4+ counts between 300 and 500 cells/μL.

Dr Volberding: Yes. The available data support the use of serial plasma HIV RNA monitoring for evaluating response to antiretroviral therapy. Even a clinically stable patient may be experiencing antiretroviral failure from, for example, the development of resistance to the drug(s). Rather than waiting for possibly irreversible overt symptomatic progression or CD4+ count decline to occur, therapy should be changed if an initial HIV RNA benefit is lost. Plasma HIV RNA levels may, in fact, be particularly useful in the patient addressed in the question, as drug failure may otherwise be so difficult to estimate. More and more evidence is accumulating to suggest that the immunologic benefits of antiretroviral therapy applied late in the disease process are incomplete. Therefore, preserving immune function by individualized, early antiretroviral therapy is of particular current interest.

Dr Katzenstein: I would add from the ACTG 175 experience, even in a stable patient with a CD4+ count of 300 to 500 cells/μL while on stable therapy, a single determination of plasma HIV RNA levels offers information about prognosis and risk over the next 3 years. A low plasma HIV RNA level (ie, <10,000 copies/mL) will provide reassurance that there is less than a 5% risk of AIDS over the next 3 years; levels higher than that should prompt consideration of additional therapy.

113. Is HIV RNA testing cost-effective? Would you consider these assays if there is no evidence of clinical deterioration?

Dr Volberding: Plasma HIV RNA testing is very rapidly becoming available as a routine clinical laboratory test in most medical centers and the costs are decreasing. The data supporting the use of HIV RNA assays are extremely strong, particularly with regard to use as a prognostic test. Titer changes in response to antiretroviral treatment are also being shown of value in retrospective and prospective surveys.

Dr Montaner: Serial viral load determinations represent a highly cost-effective approach to optimizing antiretroviral therapy. We have therefore adopted viral load–driven antiretroviral therapy within our provincial program. Data presented at the Vancouver conference demonstrate that use of viral load makes previously used laboratory tests for monitoring (ie, p24 antigen, β_2-microglobulin, neopterin, etc) redundant. Beyond this, viral load monitoring is the only way to judge the effect of therapy so that we can minimize drug exposure while optimizing the use of the drugs (and therefore resources).

Dr Katzenstein: The cost considerations are important. In the current climate, many patients are asking if they should be on a new 3-drug regimen (including a protease inhibitor), which is an expensive undertaking. For many of the reasons previously discussed, an assessment of plasma HIV RNA levels for $100 to $200 may provide a rational basis for deciding to initiate or postpone the use of a drug regimen costing $5000 to $6000 per year. The cost of an AIDS-defining OI can be very high, with hospitalization costing as much as $50,000 to $100,000. If introduction of an expensive drug reduces the risk of a clinical event by more than 50%, then the additional cost of therapy may be warranted.

114. Regarding the recently reported data on associations of HIV RNA level in plasma and risk of disease progression, can you apply cross-sectional data to prognosis and treatment decisions?

Dr Volberding: The use of cross-sectional epidemiologic data (from the MACS cohort, for example) seems appropriate for making the decision to initiate antiretroviral therapy as these data indicate the risk of progression in the untreated state. These data are not directly applicable to the use of HIV RNA assays in estimating an individual's response to a treatment strategy. That information is becoming increasingly available from trials in which HIV RNA data are compared with clinical outcome.

Dr Katzenstein: The prognostic value of plasma HIV RNA levels extends beyond the "CD4+ horizon" by providing information about risk over the next few years that is more precise than that from CD4+ counts. If the plasma HIV RNA level is low, the intensity and frequency of CD4+ count monitoring and physician visits may be reduced (eg, every 6 months). Conversely, if the plasma HIV RNA level is elevated, even in the face of a stable CD4+ count and no clinical deterioration, it may be appropriate to consider switching or adding new antiretroviral drug(s).

115. It is my understanding that the MACS data on viral load, on which the new treat-

ment recommendations rely, may be somewhat biased toward underestimation of viral load in the following ways: 1) blood was heparinized; 2) serum was not routinely separated <6 hours after collection; and 3) samples were frozen for >10 years. All these factors would underestimate what the "true" viral loads of these samples were. May we infer from this that these thresholds may not be applicable to patients today (ie, that what the MACS results indicate as a "worrisome" level may, in fact, reflect a level that was actually perhaps 5 to 10 times higher)? If so, this could lead to initiation of therapy sooner than might really be indicated, based on the "true" MACS cohort indicated levels.

Dr Volberding: It is true that the MACS data may underestimate the HIV RNA value one would expect were the studies repeated with current specimen processing recommendations. This error factor is thought to be as much as 50%; that is, the MACS numbers should be about double for thresholds in current patients. More important than the meaning of specific numbers, however, is that the MACS data show that the more virus one has, the more rapidly that person's disease will progress. By inference, these data support the use of antiretroviral drugs to attempt to control the ongoing damage caused by the repeated cycles of replication and attendant CD4+ depletion. The extension of such thinking leads to more and more confidence in treating earlier in the course of the disease. The Panel, in considering the issues, suggested that therapy be considered at a low but detectable HIV RNA titer such as one that is above 5000 to 10,000 copies/mL and that treatment be recommended when the titer (and hence, immediate progression risk) was higher (ie, >30,000 to 50,000 copies/mL). It should be noted that the *Guidelines* intentionally use *ranges* of HIV RNA levels (ie, above 5000 to 10,000; greater than 30,000 to 50,000, etc) for possible threshold levels. As noted, there is a continuum of increased risk with increasing HIV RNA levels, and as such, no single value should be considered to represent an absolute standard.

116. Please comment on the rapidity of the increase in viral load after antiretroviral drugs are stopped. In particular, comment on the importance of determining what drugs the patient is actually taking (not just the prescribed regimen) and how this could influence the interpretation of the viral load test. If the patient "ran out" of drugs a week ago, how much might that influence the test?

Dr Saag: HIV RNA levels *rapidly* return toward the original pretreatment value after antiretroviral therapy is discontinued (usually within 2 to 4 days). Therefore, it is crucial that the clinician know precisely what medications the patient was taking at the time the blood was drawn for viral load testing. If the patient had discontinued therapy, even as recently as 1 to 2 days prior to coming to clinic, there will be a profound effect on viral load level measured at that visit. Thus, an *accurate* assessment of the drugs a patient is actually taking at the time of visit is critical to interpretation of HIV RNA values.

117. The recommendations frequently refer to dropping viral load and rising CD4+ counts as therapeutic monitoring parameters. In patients with very low CD4+ counts (<100/µL), the viral load drops but CD4+ cells don't seem to rise. Is viral load drop sufficient enough to indicate therapeutic success, irrespective of a lack of CD4+ increase?

Dr Saag: The level of circulating virus in plasma is a direct reflection of ongoing replication in the host. The CD4+ lymphocyte, being a *target* of HIV replication, is an *indirect* marker of antiretroviral therapy. The CD4+ count itself is a measurement of the relative production and destruction of the CD4+ cell population. For example, if there is a production problem, either due to nutritional, toxicity, or other factors, the CD4+ count may not rise proportionately to the decrease in viral load. Thus, the change in viral load is measuring precisely the effect of antiretroviral therapy and, therefore, is our best marker of how well drugs are working or not as antiretroviral drugs.

118. How variable are the results of the plasma HIV RNA assays? Is it like CD4+ counting? Do two or three need to be done to verify rate?

Dr Saag: In general, the tests themselves vary by 0.1 to 0.2 log, and the biologic variability ranges from 0.2 to 0.3 log. Therefore, any change >0.5 log (3-fold) in viral load represents a real change in the level of viral replication within the host. It is important to note that the "minimum" of a 0.5 log change is meant to be used as a value to indicate when a drug is *not* active. It is not meant to suggest an appropriate goal for the activity of a treatment.

An important caveat, and perhaps the most important source of variability in the clinical setting, is how the specimen is processed. Plasma needs to be separated and

frozen within 4 to 6 hours after the blood is obtained from the patient. If the blood is allowed to sit at room temperature for an extended period of time (>8 to 12 hours), a significant loss of signal will occur and lead to marked variability in the results. In general, it is always a good idea to get two viral load measurements to establish the baseline value and before making a decision to change the therapeutic regimens.

119. Are there differences in the values that are obtained (ie, numbers of copies) with different plasma HIV RNA assays (bDNA, NASBA, RT-PCR, etc)? In clinical practice, we often see sudden unexplained rises or drops in viral load. Advice? Would you repeat all unexplained rises in viral loads? What, besides acute illness or vaccines, might account for "bouncing" viral loads in patients on therapy?

Dr Saag: Generally, there are differences in the absolute values of HIV RNA obtained with the different techniques. The values obtained by bDNA tend to be a bit higher than those with quantitative RT-PCR, although variability in this has been observed. In individual cases, this difference in absolute value between bDNA and quantitative RT-PCR testing can be quite substantial; however, overall, the results are usually quite comparable between the two tests (0.3-log variation). Nonetheless, most investigators recommend choosing one viral load assay and continuing with it to follow the same patient. If a change is to be made from one assay to another (eg, due to availability or cost considerations), careful assessment should be made at the time the first result returns from the new assay and serial determinations with the new assay should be sought prior to making any changes in therapeutic regimens.

Unexplained rises or falls in viral load should be confirmed with a repeat test. Acute illnesses, vaccine administration, poor specimen handling, and inconsistency of patients taking medication (noncompliance) can be associated with bouncing viral load results in patients on therapy.

120. How often should we draw viral loads on patients after they show an initial response to a regimen? Every 3 months? Every 6 months? Then if it changes/rises, do we repeat it to be sure it's real before changing therapy?

Dr Saag: Ideally, viral load determination should be repeated when the initial baseline determination is made, and then repeated within 3 to 4 weeks after initiating or making the change in antiretroviral therapy. Once an individual has demonstrated a satisfactory response, the patient should generally be followed every 3 to 4 months with repeat viral load determinations. Any significant change from the previous value should be repeated within 2 to 4 weeks to assure reliability of the new measurement before a therapeutic change is made.

121. What evidence is there that chemotherapy induced decrease in viral load has the same survival outlook as a "naturally" low viral load? Perhaps a "naturally" low viral load is simply an indication of a more intact immune system.

Dr Saag: There are very little data that indicate whether a viral load obtained as a result of chemotherapy (eg, 500 copies/mL) portends the same prognostic value as the same viral load level achieved without the use of antiretroviral therapy. However, some data are beginning to accumulate. There does appear to be a correlation between those individuals with "naturally" low viral load levels and a more efficient immune system response that seems to translate into significantly improved long-term clinical outcome. In order to equate the same level of viral load induced by chemotherapy versus the viral load value obtained "naturally," it would have to be assumed that the chemotherapy-induced viral load could be sustained for an extended period time of time with very little host toxicity. Therefore, although complete evidence is pending, it seems better for an individual to have a naturally-occurring, low viral load than a drug-induced low viral load. However, it is better to have a drug-induced low viral load than a naturally-occurring high viral load.

COST ISSUES

122. Given the cost of viral load measurements and protease inhibitors, what would you recommend for the 80% of the world who are resource poor?

Dr Saag: Serial viral load measurement should be reserved for clinical situations in which the measurement can actually have an impact on therapeutic decisions. If a clinician has very little access to medications and no drugs are available to change to when a given regimen begins to fail, it probably is not worth the expenditure of resources to routinely follow viral load. On the other hand, if therapeutic options are available, viral load measurements become quite cost effective in minimizing exposure to ineffective but expensive drugs. In rare instances, when drug supply is limited, viral load measurements may be helpful on a one-time basis to help identify individuals who would best benefit from therapy versus those in whom therapy may be deferred.

123. What strategies would you put forth to get HMOs, Medicaid, insurance companies, etc, to provide funds for viral load tests and antiretrovirals? And how would you include the pharmaceutical companies in this project?

Dr Saag: At the present time, virtually all third party payers, including HMOs, Medicaid, and Medicare, are paying for routine viral load testing. Most private insurance companies are also paying for necessary antiretroviral therapies as deemed appropriate by the treating physician. The primary difficulty in achieving access to antiretroviral therapies is within Medicaid and other government-sponsored programs. In those instances, fixed allocation of dollars has already been determined for a given population of patients. The changes in clinical treatment over the last year, which strongly advocate combination therapy with as many as three agents (some which cost $6000 or more per year), have, in essence, bankrupted the original allocation dollars to the individual programs for those patients. The best strategy to ensure increased allocation of funds to those patient populations within the government sector would be to provide detailed evidence demonstrating a true clinical benefit, including traditional measurements of benefit (eg, mortality and morbidity) as well as quality of life, patient satisfaction, and patient productivity data.

124. As an international panel, why do you make recommendations that can only be applied in Western Europe and the US (based on viral load measurements)? Why are alternative recommendations for poorer resource settings not given?

Dr Volberding: The field of HIV medicine does not exist independent of the harsh realities of the world in which we live. Poverty, discrimination, and limited access to medical care are more often the rule than the exception in this epidemic. Even in heavily endemic regions, other pressing societal concerns may take priority. The same, of course, can be said for almost all areas of medicine. How many patients with acute myocardial infections are treated within hours with thrombolytic drugs? This is not an excuse for the current recommendations, but there is no particular reason not to provide the best treatment guidelines when resources are available for their implementation as we work to develop easier, less expensive strategies that might be more relevant in regions with limited funds where HIV is, yet, a common disease. Some hope in this regard is possible with the NNRTIs, which may be considerably easier to synthesize, hence less expensive to manufacture, than the comparably potent protease inhibitors. In the end this is a political question and one that will be heard more and more loudly as we achieve real benefit from aggressive treatment strategies.

125. Could you distinguish between what you think is best to do and what you are capable of doing (such as initial triple therapy) taking into account the administrative limitations of social security, etc. In Belgium, for example, combination therapy is very difficult to obtain.

Dr Fischl: Optimal regimens should always be given whenever possible. However, several studies have now shown that didanosine monotherapy as well as combination therapies with zidovudine/didanosine and zidovudine/zalcitabine are superior to zidovudine monotherapy. Thus one option is to start with didanosine, if no other therapies are available.

Dr Yeni: It has not yet been validated that an initial 3-drug combination regimen is the best option for all patients. In any case, where the best recommended regimen is not available because of administrative limitations, one should try to adopt a treatment strategy validated in clinical trials. For example, 2-drug combinations and didanosine monotherapy have been demonstrated to be effective for initial therapy.

126. To what degree did cost consideration influence your decisions on antiretroviral therapy recommendations?

Dr Fischl: Cost did not influence our consideration, but only the current available data; this was essential for the recommendations of the best current therapies. Obviously, cost will present problems over the next several years. However, long-term vigorous therapy should result in prolonged and higher quality of life and potentially decrease transmission.

127. What are your views/recommendations/ suggestions on access to treatment in poorer countries?

Dr Saag: Each country is limited by its available resources. There is very little that most people can do to change the economic conditions within a given country in different parts of the world. Nonetheless, strategies can be initiated that determine what resources are available and utilize those resources to the best advantage for the most number of patients. This may involve routine viral load testing and establishment of specific guidelines for the type of individuals who would receive antiretroviral therapy versus those who would not, based on available resources. These criteria would vary from country to country and are dependent on the other types of resources that are available to physicians and patients in their local communities.

COMPLIANCE/ADHERENCE ISSUES

128. Which is more harmful, for a patient to miss a few doses a week, or to miss dosages for a few weeks or months altogether?

Dr Carpenter: In theory it is more harmful for a patient to miss a few doses of a protease inhibitor each week than to stop therapy entirely for periods of weeks or months. HIV resistance develops when the antiretroviral drug is present, but at levels that are too low to completely inhibit viral replication. The presence of low plasma levels of the drug would therefore be more conducive to development of resistance than prolonged periods in which the patient took no antiretroviral drug.

Dr Volberding: The effect of noncompliance of varying types may not be the same for different treatments. Although strict compliance is not thought to be essential for nucleosides alone, rigid adherence may be crucial when using more potent drugs such as protease inhibitors or NNRTIs. With the latter classes, it is probably better to stop the drug completely for a period than to chronically underdose the virus through decreasing doses or skipping treatments. The plasma HIV RNA titer may, however, provide some guidance. If a patient admits to routine nonadherence but nevertheless continues to document complete viral suppression, it may be acceptable to allow this more relaxed approach for that patient with that specific combination.

129. Compliance may be a more formidable hurdle than drug development. Comment on compliance and resistance and ways to improve compliance.

Dr Carpenter: Compliance does represent a hurdle that may be of the same order of magnitude as drug development at the present time. Inadequate compliance, especially taking a protease inhibitor in inadequate dosages, will enhance the development of viral resistance. Widespread lack of compliance would lead to increase of drug resistant viral strains in the population. There are many approaches to improving compliance. An effective approach appears to be education of patients, *by peers whenever possible*, with regard to the great benefit that is derived from the appropriate use of new combination antiretroviral regimens. Dissemination through the community of the knowledge that colleagues have benefited dramatically from three-drug combinations has enhanced the demand for, and compliance with, such regimens, despite the large number of pills and frequent dosing involved. Compliance is further improved by discussing plasma viral load results with patients, having them fully understand the goal of reducing plasma viral load to lowest possible levels.

Dr Volberding: We are only beginning to consider the issue of antiretroviral adherence and have much to learn from our behavioral medicine colleagues who have studied these issues in other chronic diseases. Certainly, adherence is easier with drugs with less frequent dosing schedules, with drugs with fewer toxic effects, and with drugs that the patient perceives to be important. We might start with these considerations in selecting otherwise equi-potent antiretroviral drugs. We must recognize that nonadherence is very common and should be addressed before and during drug therapy.

130. What percentage of asymptomatic patients will be adherent to triple therapy? For antihyperintensive monotherapy it's about 50% at best.

Dr Carpenter: It is impossible to know what percentage of asymptomatic patients will be adherent to triple therapy. It is, clear, however, that patients' full understanding of the goal of reducing the plasma viral load to the lowest possible level, and discussion of plasma viral load results with the patient at periodic intervals can be enormously helpful in enhancing adherence to triple-drug therapy. Emerging information suggest that adherence to triple drug therapy may be greater than that to monotherapy, which suggests that patients are willing and able to follow complicated regimens if they are fully aware of the benefits that can be achieved.

Dr Volberding: Again, we are only beginning to study adherence to antiretroviral therapy. The high frequency of complete viral suppression in clinical trials of protease-containing regimens does, however, suggest that compliance can be quite good. Clearly, it may be less complete in the "real world" of clinical medicine.

131. Should a known noncompliant patient be given antiretroviral therapy with the attendant risk of developing resistant viral strains and spreading these strains into the community?

Dr Volberding: It is appropriate to consider clinical settings where aggressive antiretroviral therapy might not be recommended for nonmedical reasons. As resistance to protease inhibitors or NNRTIs is almost certain to develop quickly, these drugs might not be prescribed for patients with established records of medication noncompliance. However, the benefits of such therapy should be discussed with such patients in the hope that compliance may be

supported by a stronger belief in the chance of clinical improvement. The reason to withhold aggressive antiretroviral therapy should be delineated in the medical record and can include the expectation of minimal personal benefit by that specific patient, as well as the concern that incomplete therapy might increase the community prevalence of HIV isolates resistant to effective therapies.

Dr Hammer: It should be a last resort to refuse to prescribe antiretroviral therapy to a noncompliant patient. Through a process of education, close follow-up, and the selection of an easy to take and tolerable regimen, many previously noncompliant patients can be gradually introduced to the concept of taking medications on a regular basis.

132. What do you mean by need for adherence to drug regimen? Of people I know on zidovudine, virtually everyone "takes a break" from zidovudine (maybe a weekend-free of zidovudine once every few months). But they won't tell their provider. Is this the kind of behavior that could jeopardize utility of protease inhibitors?

Dr Carpenter: Certainly lack of adherence to a multidrug regimen is a reality for almost all patients. Taking "drug holidays" is, however, not as likely to enhance the development of antiretroviral resistance as continued inadequate dosage of the antiretroviral medication. It is important to encourage optimal doses of medications at all times, acknowledging that "drug holidays" will occur.

Dr Volberding: Adherence to therapy is quite often a relative term, since few patients absolutely remember to take each and every dose as intended in the prescription. The consequences of various types of noncompliance probably vary depending on the therapy and the goals of treatment. With nucleosides alone, where the goal is partial long-term suppression, underdosing may be less a problem than intermittent therapy. With the protease inhibitors and NNRTIs, occasional periods of discontinuation may be less harmful than chronic inadequate dosing as they may predispose the patient to the appearance of high-level resistance. The provider's responsibility increasingly includes fully informing patients of the need for adherence to prescriptions.

133. More drug options and combination therapy means more widespread intolerance and noncompliance and more resistance circulating in the community. Are we soon going to be treating largely "naive" patients who have resistant viruses de novo?

Dr Carpenter: The risk of more resistant viral strains circulating in a community as a result of noncompliance presents a real problem. Lessening the impact of this problem requires both adherence to therapeutic regimens by patients, and prompt changes of drug regimen by physicians when increasing plasma viral load indicates failure of a given therapeutic regimen.

Dr Volberding: There is a definite possibility that therapy may result in the increased community prevalence of HIV with pre-existing resistance mutations. As with any antibiotic, this problem can be minimized by appropriate selection of drugs, and, with HIV, by better selection and education of patients beginning such treatments. To date, there is little evidence that this is a common clinical problem, but it almost certainly will become one in the future as more patients receive antiretroviral therapy and yet continue to engage in high-risk transmission behavior.

134. Different clinics are addressing compliance in different ways—peer-support groups, counseling upon each prescription fulfillment, withholding treatment from active drug users. Should we develop compliance guidelines, perhaps through a consensus conference?

Dr Carpenter: Different clinics are clearly addressing compliance in different ways. To a certain extent this is healthy, as problems in compliance vary with geographic region, gender, risk-taking activity and a number of other factors. Nonetheless, it may be reasonable to attempt to develop compliance guidelines, perhaps through a consensus conference, since the issue of compliance has been greatly heightened by the development of two new classes of antiretroviral agents, to both of which resistance can develop rapidly in the absence of close adherence to prescribed therapeutic regimens.

Dr Volberding: The most important issue with compliance is to understand its importance in HIV therapy, to open a dialogue with each patient, and to support calls for a linkage between physicians treating HIV and behavioral medicine experts.

STATUS OF THE *GUIDELINES*

135. Given the recent data presented in Vancouver and elsewhere, are these *Guidelines* still up-to-date?

Dr Volberding: The IAS-USA Panel *Guidelines* are definitely not out of date. While the field of HIV medicine is changing rapidly and there are an increasing number of theoretical concepts that can now be tested in clinical trials, the *Guidelines* reflect a substantial shift to the earlier and more aggressive antiretroviral therapy, including the routine use of information provided by HIV RNA assays. The *Guidelines* are more "aggressive" than most current clinical practice in the US and some of the drugs recommended are not even available in many other countries. While there are certainly physicians, patients, and investigators who personally believe in an even more aggressive approach, the Panel's recommendations are well-grounded in available clinical trial data, published and still unpublished, and in reasonable inference from information on HIV pathogenesis. Of course, these *Guidelines* are not permanent and revisions and updates are planned. Newer drugs will need to be considered as data on their clinical roles become available and clinical experience with existing combinations may enable more certainty in recommending specific treatment strategies. The Panel is confident that following its recommendations will result in improved management of HIV infection and that the *Guidelines* allow a reasonable degree of flexibility needed for individualized treatment planning.

Dr Carpenter: The *Guidelines* are based on the most up-to-date available data from controlled clinical trials of antiretroviral drugs, as modified by the most recent studies of the kinetics of HIV viral replication in humans and its alteration by antiretroviral drugs. Since there are clearly areas in which our knowledge is far from complete, the *Guidelines* provide flexibility in presenting a range of reasonable approaches in several areas (eg, when to initiate antiretroviral therapy and what to start with).

As noted in the *Guidelines* report and as discussed above, the Panel is committed to continually monitoring the results of clinical and pathogenetic studies, and to updating the *Guidelines* as these data warrant. This publication is intended to discuss the *Guidelines* and address many of the questions around their implementation.

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