Questions to and Answers from the International AIDS Society–USA Antiretroviral Guidelines Panel

From the 1st IAS Conference on HIV Pathogenesis and Treatment in Buenos Aires, Argentina

The International AIDS Society–USA Antiretroviral Guidelines Panel was initially convened in 1995 when several advances in knowledge regarding HIV biology, monitoring, and treatment were emerging. The Panel continues to update its recommendations for antiretroviral therapy for adult HIV-1 infection based on new information and drugs that are available.

It is presently known that the most effective care requires individualized management and ongoing attention to relevant scientific and clinical information in the field. At the 1st IAS Conference on HIV Pathogenesis and Treatment in Buenos Aires, Argentina, the Panel was convened to discuss evolving guidelines with an international audience of scientists and clinicians. As has been done in past issues of Topics in HIV Medicine, the Panel collected questions from the audience. Individual Panel members have provided their answers and opinions on the issues raised by the conference attendees. Many questions were addressed based on what is known about antiretroviral drugs through clinical trials, HIV patient care, and basic science. The importance of adherence, emerging long-term complications of therapy, recognition and management of antiretroviral failure, new monitoring tools, and continued evolution of the thresholds for starting antiretroviral therapy are among the most current topics of discussion in the field. In addition to the Antiretroviral Guidelines Panel members who were in Buenos Aires, we were honored to have Dr Pedro Cahn, Chair of the conference, participate in the Panel discussions.

The Panel is preparing an update of its guidelines, which will be submitted for publication in the peer-reviewed literature shortly.

Question 1: Is it still recommended that primary infection be treated, and if so, for how long, and then what?

Dr Hirsch: The rationale for treating primary HIV-1 clinical syndromes is to optimize the chances of maintaining HIV-1-specific CD4+ helper T cells, which are the major targets for HIV infection as well as the principal cells involved in orchestrating host responses against the virus. Once these cells are lost because of infection, the likelihood of developing and maintaining effective anti-HIV cytotoxic T cell responses is greatly diminished. Aggressive therapy during primary HIV-1 infection has been shown by Rosenberg and colleagues to result in maintenance of HIV-1-specific CD4+ T cells (Rosenberg et al, Science, 1997). Whether this translates to longer disease-free survival is not known. The theoretical benefit of early therapy in this situation must be weighed against the known toxicities and costs of the drugs to be used.

If it is chosen to begin therapy during the acute HIV syndrome, the goal is to inhibit virus replication as completely as possible (ie, plasma HIV-1 RNA levels below the limits of detection of the assay). How long treatment must be continued is unknown, and studies of supervised treatment interruptions in such patients are underway (Rosenberg et al, Nature, 2000).

Dr Cooper: The data on preservation of HIV-specific immunity by treating primary HIV infection are very compelling. In order to verify these outcomes we urgently need data from controlled clinical trials. Therefore, where possible, care providers should encourage their patients to enroll in clinical studies. Unfortunately, because of lack of patient and provider awareness, this phase of the illness is often missed. If this concept is proven, then the major public health issue becomes the identification of persons with primary infection by increasing surveillance and awareness by use of the detuned HIV antibody assay, for example. More recently there has been concern about transmission of drug-resistant virus, so resistance testing may have to be considered in order to optimize the initially selected antiretroviral therapy.

Question 2: Under what clinical conditions would you use a nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimen for initial therapy?

Dr Schooley: At this point I do not think there are any well worked out
clinical situations in which I would not plan to use nRTIs as part of an initial regimen. Several studies are underway or have been completed in which nRTIs have been avoided. In general, these studies have used a nonnucleoside reverse transcriptase inhibitor (NNRTI) and a protease inhibitor. Virologic results have been reasonable in these limited studies, with roughly 60% of patients with levels of HIV-1 RNA below detection at 24 weeks. Whether this approach will be more widely used in the future will depend on the extent to which the nRTI studies currently underway prove to provide durable suppression of viral replication and what we learn about longer-term effects of nRTIs. Until these data are available, nRTI-sparing initial regimens should probably be reserved for research settings.

**Dr Yeni:** A very uncommon situation could be the case of a patient with acute infection, contaminated with a virus with broad nRTI cross-resistance. In such a case, however, an NNRTI/protease inhibitor combination is not meant to “spare” nRTIs, but only to provide the patient with active drugs. There is no general recommendation for nRTI-sparing regimens for initial therapy.

**Question 3:** Is the rate of rise in HIV RNA level an important factor in choosing when to start therapy? This has not been mentioned in the discussions so far; the emphasis seems to have switched back to absolute CD4+ cell levels.

**Dr Carpenter:** Many clinicians feel that the rate of rise of HIV RNA is an indication for more frequent monitoring of the CD4+ cell count level, as a rapid rise in HIV RNA level does predict the likely rate of fall of the CD4+ cell count. However, a rapid rise of HIV RNA level is not, in itself, an indication to recommend treatment of HIV infection, as long as the CD4+ count remains above 350 cells/µL. If the CD4+ count is less than 350 cells/µL, in the face of a rapid rise in HIV RNA to a level above 60,000 copies/mL, many physicians would initiate antiretroviral therapy. You are correct in stating that the absolute CD4+ cell count level is now considered the most important laboratory guide to initiation of antiretroviral therapy, whereas the HIV RNA level alone is no longer considered to be an independent indicator for initiation of therapy.

**Dr Hirsch:** HIV replication, as measured by plasma viral load, and immunologic deterioration, as measured by CD4+ cell count, are closely linked. Although absolute CD4+ cell counts are the best immediate predictors of progression risk, the rate of HIV RNA level rises should also be monitored closely. In an individual with CD4+ cell counts between 200 and 350/µL, a rising viral load, particularly in the range above 60,000 copies/mL, would encourage me to initiate therapy before further declines in CD4+ cell counts occur.

**Question 4:** What would be the ideal dose of indinavir? Would the Panel advise indinavir 400 mg plus ritonavir 100 mg twice a day in order to decrease toxicity? Would the indinavir dose work considering the pharmacokinetic profile?

**Dr Saag:** The original FDA-approved dose of indinavir was 800 mg by mouth every 8 hours. This dose was best absorbed if given 1 hour before or 2 hours after meals but, even under these optimal conditions, there was substantial interpatient variability. Several pharmacokinetic studies have now demonstrated markedly improved pharmacokinetic parameters of indinavir when given with low-dose ritonavir (100-200 mg). This “boosted” dosing strategy allows twice-daily dosing, without food restrictions, and is associated with much less interpatient variability. Although the optimal dosing is yet to be fully worked out, most clinicians use a 100 mg (ritonavir)/800 mg (indinavir) dose given every 12 hours. When absorption is thought to be suboptimal, 200 mg of ritonavir might be used, but this dose is associated with more gastrointestinal adverse effects. Boosted indinavir doses of 800 mg twice daily are associated with higher peak (C_{max}) concentrations, which may result in a higher incidence of nephrolithiasis. Indinavir doses less than 800 mg (such as the 400 mg dose mentioned in the question) are associated with lower trough levels at the end of the dosing interval that are subtherapeutic and cannot be recommended.

**Question 5:** Would you recommend stavudine before zidovudine or vice versa? Why?

**Dr Volberding:** Stavudine and zidovudine are each extremely useful nRTIs and find their way into the care of essentially every HIV-infected patient. The drugs have comparable potency, and more cross-resistance than previously appreciated. The toxicity problems are relatively distinct, but each may cause adverse effects through mitochondrial damage. Zidovudine commonly causes anemia or neutropenia. Both drugs cause a benign macrocytosis. Although zidovudine has been associated with myositis, stavudine can cause peripheral neuropathy. Lipodystrophy and lactic acidemia may be caused by either drug, but stavudine is implicated in more reports.

The choice of which to use first arises in each patient beginning initial therapy, as one of these is employed in almost all common antiretroviral regimens. Zidovudine and stavudine have antagonistic effects and should never be used simultaneously. The choice of one or the other is based primarily on expected tolerance, toxicity, and underlying medical problems that may increase the probability of spe-
specific adverse effects. Both are good drugs and it is not possible in most cases to express a strong preference of one over the other.


Dr Yeni: It is now demonstrated that zidovudine and stavudine share common virus resistance patterns, leading to cross-resistance. Therefore, from a virologic point of view, there is no clear reason to prefer a zidovudine-then-stavudine sequence to a stavudine-then-zidovudine sequence. The choice of one or the other to start with will be dictated by underlying medical problems (eg, peripheral neuropathy) that could be predictive of a risk of toxicity higher with one drug than with the other.

Question 6: What are the nRTI combinations that should be used with protease inhibitors or NNRTIs in naive patients?

Dr Gazzard: As initial treatment often fails it is likely that a sequence of nRTIs will be given during the life span of an HIV-infected patient. The best nRTI backbone to be used first to give the optimum chance of the second regimen being successful is currently unknown and requires strategic trials. It was initially thought that mutations in the reverse transcriptase part of the viral genome following exposure to one member of the nRTI class did not reduce sensitivity to other members of this class. However, it is now clear that the accumulation of successive mutations in reverse transcriptase, as a result of continuing drug therapy despite virologic failure, does reduce the likely effectiveness of the second nRTI backbone with subsequent therapy.

Dr Montaner: It is easier to decide the right nRTI combination for a given patient than to give a broad recommendation regarding this issue. In general we rarely use zalcitabine because of its significant potential for neurotoxicity and the need for 3-times-a-day administration. There are in vitro data which suggest that stavudine and zidovudine should not be given in combination. In a recent clinical trial this concern was at least partially substantiated. There is recent evidence of increased toxicity when stavudine and didanosine were used together and therefore we are less enthusiastic about this combination at the present time. We tend not to recommend abacavir and nevirapine together as initial therapy because there is evidence that the nevirapine rash may complicate the management of suspected abacavir hypersensitivity. Most of the experience for initial therapy has been accumulated regarding zidovudine plus lamivudine, or stavudine plus lamivudine. Both of these combinations are very popular in our clinic. Zidovudine plus didanosine has been extensively studied in the past but issues of palatability related to the didanosine formulation had precluded widespread use of this combination. More recently, with the availability of an enteric-coated formulation of didanosine, this has been circumvented and in fact the newer formulation allows for once-daily dosing, which is particularly attractive for certain patients. Despite the limited data available for abacavir in the initial regimen, this agent has worked well, particularly with lamivudine or as part of a zidovudine and lamivudine triple combination. Finally, the likelihood of potential toxicities will ultimately help us to decide what is the best backbone nRTI combination for a given patient.

Question 7: What do you think about stavudine/didanosine/efavirenz compared with zidovudine/lamivudine/efavirenz?

Dr Cahn: I am not aware of large randomized controlled trials comparing these combinations. Some clinicians may prefer the zidovudine/lamivudine option, based on simplicity of the twice-a-day schedule with the fixed-dose formulation, and tolerability issues regarding didanosine. With the new formulation of didanosine (enteric coated), the stavudine/didanosine option has improved greatly. In the future, with more information regarding mitochondrial toxicity available, these options may or may not be influenced by safety issues.

Dr Hirsch: Studies comparing these 2 regimens are currently underway (eg, AIDS Clinical Trials Group [ACTG] study 384), and results will be available in 2002.

Question 8: What are the preferred protease inhibitor combinations?

Dr Cooper: Combination protease inhibitor therapy has been used in 2 main ways. In the first situation small doses of ritonavir (usually 100 mg bid) are used to boost the plasma concentrations of the active protease inhibitor by inhibiting cytochrome P450 3A4, the major isoenzyme responsible for protease inhibitor metabolism. Protease inhibitors that can be boosted in this way are saquinavir (generally dosed at 1000 mg bid), indinavir (800 mg bid), amprenavir (600 mg bid), and lopinavir (400 mg bid coformulated with ritonavir). Usually the plasma trough levels of the protease inhibitor are greatly enhanced above the IC50 level for the virus through all of the dosing inter-
val. This is much more reliable than single protease inhibitor use. Nonetheless, pharmacokinetic monitoring is recommended especially if additional drugs that affect cytochrome P450 metabolism are used.

The second way of using double protease inhibitors is as a combination in which both drugs are given at doses that have anti-HIV activity. Given the ability of some protease inhibitors to salvage a failing protease inhibitor regimen, this is a biologically plausible approach. It has been well studied for ritonavir/ saquinavir and to a lesser extent for ritonavir/indinavir but there is no good evidence to prove that double protease inhibitor-based regimens are superior to single protease inhibitor-based regimens.

**Question 9:** Given the recent data presented at this meeting, what is the role of hydroxyurea in the management of HIV-infected individuals?

**Dr Montaner:** As pointed out by Murphy and colleagues (Abstract 450) from Northwestern University, the results of the 3D study seem to offer some hope that we may be able to define the role of hydroxyurea as an adjuvant in selected groups of patients, particularly in the context of drug-resistant viruses. In the 3D study, treatment-experienced patients randomized to hydroxyurea had better virologic outcomes despite higher toxicity rates. Hydroxyurea blunted the absolute CD4+ cell count responses but not the CD4+ percentage increases. Lower doses of hydroxyurea should be considered for further study in treatment-experienced patients with virologic failure in order to determine if we can retain the virologic effect but avoid the excess toxicity seen in the 3D study. Until these issues are resolved, the use of hydroxyurea should be limited to the experimental setting.

**Dr Richman:** It is important to emphasize no proven role for hydroxyurea has been identified. Although it does appear to show virologic benefit in some studies, it does blunt CD4+ responses and it does have significant toxicity.

**Question 10:** When would the Panel recommend treatment interruption for a patient who is not experiencing adverse events, has good tolerance, and has a viral load below 50 copies/mL? All trials about this issue show increased viral load (though not significant increases). But a viral load of below 50 copies/mL is not the same as a viral load above 1000 copies/mL.

**Dr Saag:** The situation where treatment might be interrupted in a patient with good tolerance, no adverse events, and a viral load less than 50 copies/mL is when the patient had originally been started on treatment (years ago) with a viral load and CD4+ cell status that would clearly not warrant initiation of treatment today. In 1996, the mantra for the initiation of therapy was to “treat early, treat hard.” This was based in large part on the concept that complete blocking of viral replication could lead to eradication of HIV within 3 to 4 years. More recent evidence suggests that even a complete block, sustained for up to 60 years, will not lead to eradication of all latently infected cells from the body.

With the increasing recognition of long-term complications of therapy, including the potentially fatal (though rare) cases of lactic acidosis, many clinicians are now suggesting that patients whose original baseline CD4+ counts were over 500 cells/µL (and especially if their original viral load value was low, e.g., <20,000 copies/µL) consider stopping therapy and going on a “supervised” treatment interruption.

Strong emphasis should be placed on the supervised nature of this interruption. Once patients stop therapy, checks of CD4+ counts and viral load values should be made monthly for 2 to 3 months and then every other month for 6 months in order to assure there is no precipitous decline or increase in CD4+ counts or viral load, respectively.

**Dr Gatell:** Treatment interruptions should be considered clinical research, not routine clinical practice, and only performed in the setting of well controlled clinical trials. In responding patients (viral load <50 copies/µL), interruption may be considered when the actual CD4+ cell count is above the current recommendation for initiation of antiretroviral therapy, and the situation is even better if the lowest CD4+ cell count has never been below the current recommendation for initiation of antiretroviral therapy.

If antiretroviral therapy is interrupted, viral load most likely will rebound and this may represent an increased likelihood of HIV transmission in cases of unprotected risk practices. This public health concern should be balanced with the potential individual benefit associated with less drug exposure.

**Question 11:** In my 13 years of experience in the Johannesburg Hospital HIV Clinic, I have noticed that a significant number of patients (approximately 7%-10%) have a steady decline in CD4+ cell numbers for 4 to 6 years from about 200 to 300/µL or so and then stabilize after a few years at a lower level. Why does this happen?

**Dr Schooley:** It is difficult to answer this question without knowing whether you are referring to patients who are on or off antiretroviral therapy and, if on therapy, the extent to which viral replication has been controlled. If you are speaking of a situation with patients on optimal viral suppression (i.e., with HIV-1 RNA levels <20-50 copies/µL) over the period in question, I would have to say that most patients I have encountered have either had stable...
or gradually rising CD4+ cell counts and a noticeable decline over the long term has been an unusual experience.

**Dr Cooper:** This observation that you have made is inconsistent with the known natural history of HIV disease. Untreated persons with HIV infection lose approximately 50 to 60 CD4+ cells/µL per year. The rate of decline is steady until in some patients there is a change from non-syncytium-inducing to syncytium-inducing viral phenotype when the rate of decline often accelerates. In some patients the biological noise generated by frequent measurement of CD4+ cell counts may give the false impression of stabilization. I am unaware that HIV-infected populations in the developing world have different CD4+ count trajectories but clearly your observation should be followed up with more prospective data.

**Question 12:** Is it justified to put a patient with CD4+ cell count of 284/µL and plasma viral load of 72,000 copies/mL on highly active antiretroviral therapy (HAART)? In India, we would wait and watch without HAART and I think the patient would do better in the long run. We would initiate HAART when his CD4+ cell count declines to below 200/µL and his HIV RNA is 100,000 copies/mL.

**Dr Richman:** Not only is it justified, it is recommended. Data from the Multicenter AIDS Cohort Study (MACS) would predict that patients with more than 30,000 copies/mL of HIV RNA plasma lose on average 76 CD4+ cells/µL per year. This patient is entering the range of CD4+ cell count values in which the risk of AIDS-related diseases begins to increase. Thrush, infections with herpesviruses, and other symptomatic complications also develop in such patients. The risk of delaying therapy also includes a diminished probability that the treatment will produce a viral load response to below detection limits of the assay. The ability of treatment to produce an HIV RNA level below detection limits progressively diminishes with lower CD4+ cell counts and higher HIV RNA values. It should also be pointed out that the patient’s HIV RNA value may not significantly increase in the absence of treatment. Many patients die whose HIV RNA values have never exceeded 100,000 copies/mL. The value of HIV RNA determines the rate of CD4+ cell decline, but a low CD4+ count (eg, 100 cells/µL) confers the same risk whether it was achieved quickly or slowly.

**Dr Hirsch:** Patients who have CD4+ cell counts below 200/µL and HIV RNA levels above 100,000 copies/mL are at substantial risk for rapid progression. A CD4+ cell count of 284/µL with a plasma viral load of 72,000 copies/mL is getting dangerously close to those thresholds, and large cohort studies suggest that therapy is indicated at those levels. Other factors, such as patient preferences and rate of change in CD4+ cell counts or viral loads, should also be considered.

**Question 13:** How would you manage a patient who has been HIV-seropositive for 15 years, and has taken almost all medications, including zidovudine, lamivudine, stavudine, indinavir, nelfinavir, amprenavir, efavirenz, and adefovir? Now the patient is on lamivudine/stavudine/efavirenz/amprenavir/ritonavir. Genotype results show resistance to all drugs except lopinavir and adefovir. Viral RNA is rising from below 50 to about 10,000 copies/mL and CD4+ cell count is stable at 400/µL. What do you recommend?

**Dr Saag:** In order to best answer this question, it is important to know what was the patient’s original baseline (pretreatment) HIV RNA value. If the current viral load is more than 0.5-log (3-fold) below the pretreatment value, there is strong evidence that the patient is not likely to progress clinically over the next 3 to 6 months. In this instance, it is very reasonable to continue the patient’s current regimen. The principal risk to this approach is the likelihood that further resistance-conferring mutations will accumulate; however, since this patient has already developed a virus with multiple resistance mutations, the prevention of resistance development is no longer the primary goal of therapy and prevention of clinical progression is now the sole objective. In many clinical situations such as this, the pretreatment viral load value is not known. In that setting, the patient could either stop therapy for 2 to 4 weeks to roughly establish the viral load “set point” (natural baseline) for that patient or the patient could continue with the current regimen until there is some decay in the CD4+ cell count.

Either approach is acceptable, though with the latter it is important to check CD4+ cell counts more often, eg, every 6 to 8 weeks. If it is decided to change the regimen, my approach would be to anchor the regimen with the 2 agents with the highest degree of susceptibility (in this case, lopinavir and tenofovir, if available, which may have a resistance profile similar to the no-longer-available drug adefovir) and fill out the regimen with other agents that the patient has tolerated well in the past. In either scenario, it is critical to discuss options with the patient and chart the course together.

**Dr Montaner:** It should be noted that prior exposure to most or all medications and even cumulative evidence of viral load rebound with all available medications will not preclude achieving a sustained plasma viral load level below detection with the use of multidrug therapy. This approach has been applied in our clinic with considerable success. We generally think that in the absence of a clear therapeutic option, in a patient who is at high
risk for short-term disease progression with evidence of 3-class resistance and objective evidence of viral load rebound with most if not all available drugs, a therapeutic trial with multidrug rescue therapy may be considered. Obviously, the patient’s preference as well as comorbidities and history of toxicity should be considered carefully before undertaking such a course of action.

Question 14: When would you consider initiating an STI? At what viral load and CD4+ cell count? When would you reinitiate therapy and at what viral load or CD4+ cell count? When you reinitiate, would you go back to the initial regimen?

Dr Volberding: Structured or strategic treatment interruption (STI) has raised many practical and theoretical questions. As a way of re-exposing the immune system to HIV antigens after periods of prolonged suppression on successful antiretroviral therapy, STI becomes a form of auto-vaccination. This strategy has worked well in a preliminary study in patients with acute or extremely recent HIV infections. The results in established infection have been less promising. I would not recommend STI in these patients outside of carefully controlled clinical trials.

Another form of STI is to temporarily stop antiretroviral drugs in patients with advanced virologic failure in whom HIV has become resistant to all drugs. Here, STI is used to allow an overgrowth of drug-selective, wild-type HIV. Although this strategy may allow a brief period of resuppression of virus, failure occurs rapidly unless new drugs that do not have cross-resistance can be used.

A final type of STI, named structured intermittent therapy (SIT), has recently been suggested by National Institutes of Health investigators. Here, therapy is used intermittently, for example on alternate weeks, simply to decrease or delay cumulative drug doses and hence toxicity. Again, this must be seen as a research strategy and cannot be recommended apart from controlled trials.

Dr Montaner: I fully agree with Dr. Volberding’s overview of this very difficult topic. We think that the recent enthusiasm with regard to the use of STI should be tempered by the lack of efficacy data and more importantly safety data in support of it, particularly as it pertains to the long-term implications of this therapeutic maneuver. We do not routinely use STI in our clinical practice, but we have been fairly liberal in considering a patient’s wishes in terms of indeterminant treatment interruptions, if a patient had started effective antiretroviral therapy with what today we would consider a relatively benign laboratory profile. Data from our group and others have suggested that the 2- to 3-year AIDS-related morbidity and mortality rates are quite low as long as effective antiretroviral therapy is initiated at CD4+ cell counts over 200/μL, regardless of plasma viral load. In contrast, there is a definitive risk for toxicity and evolution of resistance, which has led us to reassess the risk-benefit ratio of aggressive early intervention with currently available therapies.

Question 15: The patient is a 44-year-old man in his fifth year of taking zidovudine/didanosine/nevirapine. Since introduction of viral load tests that detect levels of 40 to 50 HIV RNA copies/mL of plasma, he has had detectable viremia of a few hundred copies/mL. He experimented with efavirenz but could not tolerate the drug, so he returned to nevirapine and intensified his regimen with abacavir. Detectable viremia persisted at similar levels but for the past 9 months has bounced between 400 and 8600 copies/mL with no clear trend. The CD4+ cell count is consistently stable around 300/μL. Two genotype test results indicate resistance to zidovudine, didanosine, and nevirapine.

Would you recommend now changing to lopinavir/ritonavir/lamivudine/tenofovir or something else? Would you recommend changing only when viral load is clearly on a rising trend above 10,000 copies/mL or on evidence of further evolution of resistance? Or change the regimen according to some other criteria?

Dr Richman: The risks of continuing a failing regimen are the progressive increase of resistance to the nRTIs that the patient is taking and increase in cross-resistance to the whole class of drugs. Sticking with a failing regimen makes little sense unless there are limited alternatives. This patient has alternatives and if his CD4+ cell count drops significantly, he is at risk for HIV disease progression. I think your proposed regimen is as good as any, and to wait would only limit future options.

Dr Gazzard: Optimal therapy in this case is bound to remain a matter of opinion as there is no evidence base on which to guide us. The danger of continuing the present therapy is that, almost inevitably, further mutations in the viral genome will emerge that will increase the “fitness” of the virus under the selective pressure of the same drugs. This is likely to be associated with a rising viral load and a falling CD4+ count. There is no evidence that this would impede the future response to protease inhibitors.

The main issue would therefore be whether or not further mutations would reduce the sensitivity to lamivudine, to which he has not been exposed previously, or to tenofovir. Available data indicate that virus with mutations producing reduced sensitivity to nRTIs remains sensitive to tenofovir unless a codon 210 or 41 mutation emerges (associated with reduced sensitivity to zidovudine) or a codon 69 muta-
tion emerges (coding for multiple serine insertions that reduce sensitivity to all presently available nRTIs).

My view would be that in this particular individual, the CD4+ count indicates that his short-term risk of opportunistic infections is small and the risk of development of resistant mutations to lamivudine and tenofovir is also small; therefore I would continue present therapy with frequent monitoring of his CD4+ count until this showed a clearly downward trend.

**Question 16:** In Bolivia we only have zidovudine and zalcitabine. Can you initiate either or both of these drugs in patients with clinical symptoms? The CD4+ cell count is not accessible to everyone.

**Dr Cahn:** In this difficult scenario, I would defer therapy until the latest moment, which without CD4+ cell counts is to be identified by clinical symptoms (AIDS-defining diseases or oral thrush, hairy leukoplakia, unexplained fever, diarrhea, weight loss, etc).

In no case would I use either zidovudine or zalcitabine in monotherapy.

**Dr Katzenstein:** The best data we have in this setting is from the Delta and ACTG 175 trials where the combined use of zidovudine/zalcitabine was better than zidovudine alone. I agree with Dr Cahn that treatment with dual nRTIs in this setting should be delayed until there are clinical symptoms, to optimize the use of the drugs. If it is possible to obtain didanosine and stavudine through the sponsor's access program (publicly announced at a cost of US $1.00/day) this combination may be a less expensive dual nRTI combination with fewer adverse effects than zidovudine and zalcitabine.

**Question 17:** A 50-year-old patient diagnosed HIV-seropositive has a CD4+ cell count of 100/µL and viral load 400,000 copies/mL. After 3 months of lamivudine/zidovudine plus indinavir, the patient's CD4+ cell count is 150/µL and viral load is 500 copies/mL. How should treatment proceed?

**Dr Gatell:** This is a patient with a fairly advanced HIV-1 disease who started triple therapy including a protease inhibitor (indinavir) with a reasonably good response at 3 months. My advice would be to continue with the same therapy and to check the situation at 6 months. If by then viral load is below detectable levels and CD4+ cell count continues to rise, one may consider the possibility of simplifying therapy depending on the tolerance and preferences of the patient. Reasonable options to simplify might be replacing indinavir with efavirenz or with abacavir (fixed-dose lamivudine/zidovudine/abacavir).

**Dr Gazzard:** I think it is clear that 12 weeks on initial antiretroviral therapy is too soon to decide whether such therapy is working when the viral load was 400,000 copies/mL prior to treatment. Indeed, a viral load of 500 copies/mL would imply that the plasma virus will almost certainly fall below detectable limits within the next 4 to 8 weeks. A more difficult question is whether or not indinavir, combined with zidovudine and lamivudine, is the optimum initial regimen. Randomized controlled trials with clinical endpoints indicate an improvement in outcome using this therapy, and a subgroup of such patients had advanced HIV infection. Comparable experience using other therapies initially in this group of patients is limited. Although many would use indinavir combined with ritonavir for pharmacokinetic enhancement to simplify the regimen, there is an increased risk of side effects. I would personally still use a double nRTI/NNRTI combination as I am impressed by the relative freedom from adverse effects, the “forgiveness” of such a regimen, and the ease of adherence. This, in my mind, more than compensates for the relative lack of clinical controlled trial evidence for efficacy in this particular group of individuals.

**Question 18:** In resource-poor settings, when CD4+ cell counts and clinical response are adequate and patients on adefovir are doing well in spite of a not-to-good decrease in viral load count, why not avoid frequent measurements of rise so that expensive tests are avoided?

**Dr Katzenstein:** The issue of “how much monitoring is enough” where there has been a good clinical, but a minimal virologic, response to antiretroviral drugs is difficult. In resource-constrained settings there is little reason to monitor virus load, particularly when further options for new treatments are limited and the cost of virus load testing is significant. However, the same is not true for toxicity monitoring. If, for example, adefovir were being used as treatment and there is a “good clinical response,” I would suggest frequent, inexpensive assessments of electrolytes and renal function. The single test and strategy that may help decide whether to continue treatment is observing clinical and CD4+ changes with the discontinuation of antiretrovirals.

**Question 19:** Is there rationale to use lamivudine in patients carrying an M184V mutation, especially in patients in whom numerous drugs have caused multiple failures? Are other options available?

**Dr Katzenstein:** Although there have been no prospective randomized trials completed that have directly addressed this important salvage question, many physicians continue to use lamivudine, generally in combination with either zidovudine or stavudine in salvage.
regimens. The rationale for the continued use of lamivudine in patients with the M184V mutation and multidrug failure comes from randomized trials of nRTI therapies including lamivudine (ACTG 302 and 303). These studies have shown that on average, patients who continued on a “failing regimen” including lamivudine sustained more than a 0.5-log (70%) reduction in HIV RNA from baseline after 48 weeks, even though the M184V (or I) mutation had emerged in the virus of most. One explanation for this may be found in phenotypic studies of viruses from highly nRTI-experienced subjects that show that the M184V mutation “re-sensitizes” viruses to thymidine nRTIs, reducing high-level zidovudine resistance by nearly 10-fold and stavudine resistance by 50%.

In contrast, there is clear evidence that the M184V mutation increases resistance to didanosine and abacavir in the presence of multiple thymidine nRTI mutations. These data provide a rationale for the continued use of lamivudine, although with the caveat that the continuation as well of either zidovudine or stavudine is important to this activity. Triple-nRTI regimens, whether zidovudine/didanosine/lamivudine, stavudine/didanosine/lamivudine, or fixed-dose lamivudine/zidovudine/abacavir appear to exert continuing virologic activity, despite the presence of resistance to each of the drugs in the regimen, including the M184V mutant.

An upcoming option for reverse transcriptase inhibition as part of a regimen in patients in whom multiple drugs and classes have failed is the addition of the nucleotide reverse transcriptase inhibitor (nRTI) tenofovir. Like adefovir, this compound demonstrates activity against M184V-containing viruses and may be useful in continued treatment of patients in whom multiple nRTIs have failed.

The inclusion of multiple nRTIs in a salvage regimen depends on the tolerance, toxicities, and cost of the drugs, as well as evidence of benefit.

**Question 20:** When would you recommend postexposure prophylaxis? Which regimen would you select? When would you stop postexposure prophylaxis?

**Dr Yeni:** Postexposure prophylaxis (PEP) is recommended when the risk of transmission from an occupational or non-occupational exposure is significant. A high risk of transmission following occupational exposure results from blood or fluids containing blood, or potentially infectious fluids or tissue from a patient with HIV infection documented or likely, coming into contact with a mucous membrane or not-intact skin, or through percutaneous injury or bites resulting in blood exposure. A significant risk of transmission following non-occupational exposure results from unprotected sexual intercourse or sharing drug injection equipment with a patient with HIV infection documented or likely. In case of non-occupational exposure, prophylaxis is recommended in the absence of predicted, recurrent HIV exposure, or if a decision to engage into risk-reduction practices is taken.

PEP should be started as soon as possible after the exposure, and in all cases within 48 hours. Once initiated, PEP should be continued for 4 weeks if tolerated, unless the source patient with an unknown HIV serostatus when PEP was started, is determined to be HIV-seronegative.

The regimen of choice, in the absence of HIV drug resistance, remains debated but a systematic triple-drug combination may be warranted in order to simplify recommendations (rather than selecting a double- or triple-combination according to the level of exposure risk), and to achieve the highest antiretroviral activity. The use of drugs that may be responsible for severe adverse events (such as nevirapine or abacavir) should be discouraged. Efavirenz should not be used in women of childbearing age, because of the potential of teratogenic effects.

**Dr Cahn:** This is quite a difficult issue, since any current or future recommendation is to be based on our best guess, and since controlled clinical trials are not feasible, neither in the occupational nor in the sexual exposure setting. In our practice, we follow the Centers for Disease Control and Prevention (CDC) guidelines for health care worker injuries, trying to provide counseling and support to the injured health care worker. Regarding sexual exposure, we encourage rape victims to take a triple-drug prophylaxis regimen for 1 month. The rationale is that in the vast majority of attacks, the serostatus of the offender is unknown, and frequently violence is involved, increasing the risk of mucosal damage. Regarding the drugs to be selected, again, no controlled clinical trials are or will be available. The CDC has released recommendations against nevirapine use in the occupational setting. Abacavir hypersensitivity reaction is diagnosed in around 4% to 6% of cases, and has not been linked with high CD4+ cell levels, as some studies showed in the case of nevirapine. Simplicity of I pill taken once daily, allowing potentially better tolerance and adherence, has to be weighed against the potential of a hypersensitivity reaction. Potency is a matter of debate in patients with plasma viral loads higher than 100,000 copies/mL, but this may not be relevant in the setting of prophylaxis, as we learned from zidovudine efficacy in prophylaxis of mother-to-child transmission. So, a strong recommendation against should only be applied to nevirapine and to ritonavir (full dosage 600 mg bid), due to toxicity and tolerance respectively.

**Question 21:** Should efavirenz be used in women of child-bearing age who plan to become
pregnant in the near future but are using only condoms for contraception?

**Dr Carpenter:** Primate data indicate that serious central nervous system abnormalities occur with the administration of efavirenz during the first trimester of pregnancy. Since condoms are far from “100%” effective in preventing pregnancy, I advise women not to utilize efavirenz in this situation.

**Question 22:** An HIV-seropositive woman had been on zidovudine/lamivudine/indinavir, but stopped the drugs for 2 years. She is now 2 months pregnant. What drugs would you recommend now?

**Dr Schooley:** Prevention of perinatal transmission of HIV-1 infection is best accomplished by crafting a regimen for the mother to which the virus is likely to be susceptible and providing the infant with effective postexposure prophylaxis. In this case, it would be important to know the full details of the mother’s prior antiretroviral chemotherapeutic experience. Was zidovudine/lamivudine/indinavir the only regimen she had previously received? How successful was it in suppressing virus during the time she received it?

If the data strongly suggest that her virus was “fully” suppressed while she received this regimen, one could expect that her virus would be susceptible to these drugs at this point in time. On the other hand, if she had previously received zidovudine monotherapy to which lamivudine and indinavir were sequentially added, one would be concerned that she might harbor virus that is resistant to 1 or more of these drugs.

Because of competition between wild-type and drug-resistant virus, it could be possible that drug-resistant virus would not be detectable in the plasma or in the lymphoid reservoirs with currently available techniques. Because of these factors, the selection of a specific regimen cannot be made on the basis of currently available data. If she, indeed, had not been on other drugs prior to her zidovudine/lamivudine/indinavir experience and if the virus was fully suppressed by these drugs while she was on therapy, it would be reasonable for these drugs to be reinstated in the context of her pregnancy. If there are concerns that prior drug exposure might have selected for resistance, alternative drugs should be selected.

Resistance testing should be employed in the selection but it should be noted that this testing might miss minority species or archived virus that was replaced in the plasma by competition with wild-type virus.

**Question 23:** A patient is taking stavudine/didanosine/efavirenz plus antituberculosis treatment. She presents with hepatotoxic encephalopathy and drugs are suspended. How should treatment continue? Should antiretroviral therapy be reinstated? Hepatic enzymes are now normal, the patient is asymptomatic, and does not have hepatitis B or C virus infections.

**Dr Carpenter:** The presentation strongly suggests that the patient’s encephalopathy was directly related to hepatitis caused by administration of drugs. Since the hepatotoxicity was more likely caused by the antituberculosis medications than by the antiretroviral medications, it would be appropriate first to reinstate the antiretroviral therapy that the patient was originally receiving, with close monitoring of the liver enzymes and bilirubin levels.

If the patient had active tuberculosis, it would also be appropriate at this time to reinstate treatment with streptomycin and ethambutol, the 2 antituberculosis agents least likely to cause hepatic damage, as a holding regimen. Then if no hepatic abnormalities developed over a period of 4 weeks, it would be appropriate to add rifampin with continued close monitoring of the hepatic enzymes. If no hepatic abnormalities developed over an additional 4-week period, it would be reasonable to add isoniazid, with continued close monitoring of hepatic enzymes. (Pyrazinamide is the most hepatotoxic of the frequently-used antituberculosis drugs, and it should probably not be reinstated at any time in the management of this patient).

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