

**Special Contribution****Current Strategies for Antiretroviral Therapy:  
Panel Discussion of Clinical Cases**

*As part of an International AIDS Society–USA course in Atlanta in March 2002, course faculty participated in an interactive panel discussion addressing strategies for managing antiretroviral therapy. Michael S. Saag, MD, and Jeffrey L. Lennox, MD, presented cases and moderated discussion of clinical questions by an 8-member panel (see list of panel members below), as well as comments from the audience. The following article summarizes selected comments drawn from the discussion of clinical cases.*

**Case 1**

*A 44-year-old man is found to be HIV-seropositive during a routine insurance exam. He has a history of hypertension, which has been controlled with diet. He understands the benefits and complications of antiretroviral therapy and is ready to start therapy at your recommendation. His plasma HIV-1 RNA level is 30,000 copies/mL and his CD4+ cell count is 350/μL. Do you recommend starting therapy?*

**Dr Thompson:** We have struggled for years with the question of when to start therapy and there still is no certain answer. It is clear that therapy should be initiated once the CD4+ cell count drops below 200/μL. Current guidelines state that in patients with plasma HIV-1 RNA levels as low as 30,000 copies/mL and CD4+ counts above 350 cells/μL, it may be reasonable to defer therapy and monitor. The CD4+ count range between 200 and 350 cells/μL is a gray area.

**Dr del Rio:** If this patient had said that he is undecided about antiretroviral therapy or that he is not ready to start, I would explain that we could wait, monitor his laboratory results, and plan to initiate therapy before the CD4+ cell count reaches 200/μL. However, since he stated that he is ready to start therapy, I would be comfortable recommending antiretroviral therapy at a CD4+ count of 350 cells/μL.

**Dr Lennox:** At 30,000 copies/mL, this patient's viral load is in the intermediate range and does not indicate initiation of therapy. We are still learning which drugs are associated with long-

term metabolic complications, one of the main adverse effects of antiretroviral therapy. In the next few years we may know more about the causes of these complications and how to prevent them, and some of the newer agents becoming available may be less likely to be associated with known adverse effects. In this case, it might be reasonable to wait to initiate antiretroviral therapy and monitor the CD4+ cell count and viral load.

**Dr Saag:** Current treatment guidelines recommend less emphasis on viral load and much more emphasis on the CD4+ cell count for monitoring disease progression. Earlier data and guidelines supported an emphasis on the use of viral loads, but those data were from untreated patients and reflect the natural history of HIV disease before therapy. In the era of highly active antiretroviral therapy (HAART), the CD4+ cell count appears to be the more important of the 2 laboratory tools.

In their cohort study, Montaner and colleagues demonstrated that among patients starting their first HAART regimen, 91% of those with baseline plasma HIV-1 RNA levels above 200,000 copies/mL survived at 2 years. In comparison, among patients with baseline CD4+ counts below 50 cells/μL, 78% were alive at 2 years. Data from the Multicenter AIDS Cohort Study (MACS) suggest that the viral load serves as an indicator of how rapidly the CD4+ cell count will fall per year. In general, patients with higher viral loads will experience a more rapid decline in CD4+ cell counts than those with lower viral loads.

**Dr Gulick:** Many people have referred to these cohort data as evidence that we could delay starting antiretroviral therapy in all patients until the CD4+ cell count is below 200/μL. I think that this is a misinterpretation of these data because the end point in this analysis was the proportion of patients surviving. In fact, I do not think that these data support deferral of therapy until the CD4+ cell count is 200/μL because of the increased risk of death, particularly in those with plasma HIV-1 RNA levels greater than 100,000 copies/mL.

**Dr Saag:** Chen and colleagues conducted a similar study at the University of Alabama at Birmingham, but had 4 years of patient follow-up. At 2 years, 78% of patients with an initial CD4+ count

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below 50 cells/ $\mu$ L were alive. For patients with 200 to 350 CD4+ cells/ $\mu$ L, survival at 2 years was approximately 97%. At 4 years, the survival rate was 65% among patients starting HAART with a CD4+ count below 200 cells/ $\mu$ L. These data also suggest that waiting for a CD4+ cell count of 200/ $\mu$ L is too late.

**Dr Thompson:** Monitoring the CD4+ cell percent value is also important. All of our data tend to focus on absolute CD4+ cell counts. We see patients with *Pneumocystis carinii* pneumonia (PCP) who have CD4+ cell counts of 300 to 350/ $\mu$ L and CD4+ cell percent values of 12% to 14%, as was shown in the original data on PCP prophylaxis. It is important to take into account that patients with a CD4+ cell count of 300/ $\mu$ L might have a percent of 12, which is essentially equivalent to a lower CD4+ cell count.

**Dr Lennox:** In some places, the question of starting antiretroviral therapy at 350 CD4+ cells/ $\mu$ L or waiting until 200 CD4+ cells/ $\mu$ L is moot. In Atlanta, by the time most patients are diagnosed as HIV-seropositive, they already have clinically defined AIDS or advanced disease. This tendency for late presentation raises an important challenge: how do we encourage people to be tested earlier? We frequently see patients who are ultimately diagnosed with HIV-related PCP but who had presented to the emergency department, walk-in clinic, or some other medical clinic within the past year or two and had not been tested for HIV.

**Dr Saag:** I would add that if the decision is to initiate therapy, it is important to take adherence issues into account immediately, at the time of initiation of the first antiretroviral therapy regimen. We will not know in advance if a patient will tolerate one particular drug or another, but it is important to try to tailor the regimen based on potency and likely tolerability. Some considerations include history of neuropathy, gastrointestinal intolerance, and diarrhea. In our experience, stopping the first regimen because of virologic failure is uncommon; more typically, patients stop because of toxicity or tolerability issues. Chen and colleagues showed that among people on their first HAART regimen, only 66% are still on that first regimen after 1 year, and only 33% are still on the regimen after 3 years; at the end of the second year of HAART, 14% to 15% of patients are on their fourth regimen.

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## Case 2

*A 26-year-old man presents with PCP and is diagnosed with HIV infection. His CD4+ cell count is 33/ $\mu$ L and his plasma HIV-1 RNA level is greater than 750,000 copies/mL. He does not have any other medical or mental health problems. Would you start antiretroviral therapy? With how many drugs? Which ones?*

**Dr del Rio:** This is a fairly typical case of the presentation of advanced HIV disease. There are some data suggesting that an initial 4-drug regimen may be better than a 3-drug regimen in patients presenting with advanced HIV disease. Analysis from

AIDS Clinical Trials Group Study 388 by Fischl and colleagues shows that among patients taking 2 nucleoside reverse transcriptase inhibitors (nRTIs) and indinavir, 2 nRTIs and nelfinavir plus indinavir, or 2 nRTIs and efavirenz plus indinavir, the group that took the latter regimen had a better virologic response than the other groups. These findings suggest that this patient should perhaps start with 4 drugs, including a protease inhibitor and an nRTI, but we do not have a lot of clinical trial data on this issue.

**Dr Saag:** The data on using 2 drugs plus lopinavir/ritonavir are promising, and this regimen seems to work in patients with higher viral loads. There also are data on 2 drugs plus efavirenz suggesting that this regimen is effective in patients with higher viral loads. I think that current data suggest that a regimen of 3 nRTIs is not as effective in patients with plasma HIV-1 RNA levels above 100,000 copies/mL.

**Dr Gulick:** We do not have enough information on this issue. There are some initial data from 2 studies that evaluated a triple nRTI regimen and a regimen of 2 nRTIs and indinavir. There are practitioners in New York who will swear by a combination of fixed-dose lamivudine/zidovudine/abacavir and tenofovir or fixed-dose lamivudine/zidovudine/abacavir and efavirenz, but we do not have the clinical trial data to support this. There are numerous studies showing that 3 drugs are more effective than 2 drugs, but in studies of 4 drugs versus 3, it is not clear which option is better. In one study, Eron and colleagues showed that 3 drugs actually were better than 4 because most of the people taking 4 drugs simply could not tolerate them as well.

**Dr Lennox:** We may never know if 4 drugs are better than 3 in advanced-stage disease because there are always new regimens emerging, so the comparison regimens become obsolete.

**Dr Thompson:** There are some small studies evaluating fixed-dose lamivudine/zidovudine/abacavir and a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor (NNRTI) as an initial therapy in patients with higher viral loads. Once the patient's viral load is suppressed for approximately 6 months, he or she continues on fixed-dose lamivudine/zidovudine/abacavir without the protease inhibitor or the NNRTI. These studies are not well-controlled, but it is a strategy that people are using. The advantage may have to do with adherence to the regimens over time.

**Dr Saag:** The bottom line is that the potency of the first regimen is crucial. We must choose regimens that are likely to reduce the plasma HIV-1 RNA to less than 50 copies/mL. At the same time, drugs have no potency if they are not taken, so adherence is an equally important factor in choosing the first regimen.

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## Case 3

*A 73-year-old HIV-seropositive woman has been taking stavudine/lamivudine/efavirenz for approximately 2 years. Her plasma*

*HIV-1 RNA level, which was consistently less than 50 copies/mL, has increased to approximately 6500 copies/mL. A genotype shows the M184V mutation but virus is otherwise wild-type. Would you add or replace an nRTI, add a protease inhibitor, add a new nRTI and a protease inhibitor, or recommend something else?*

**Dr Saag:** A couple of years ago, we would have said “stay the course,” but there are now compelling data that show that when the M184V mutation is the first nRTI mutation to emerge, subsequent mutations will follow. Whether to change or add drugs depends on how this patient is tolerating the regimen and how adherent she is. Typically, you might not discontinue lamivudine, but assuming her adherence is good, you might intensify the regimen by adding tenofovir. That would involve just 1 extra pill per day and would not add any significant risk for new resistance mutations, especially if her plasma HIV-1 RNA level returns to less than 50 copies/mL.

**Dr Gulick:** We could also argue to change 2 drugs in this patient’s regimen. By adding 1 drug to the regimen in someone with a plasma HIV-1 RNA level of 6500 copies/mL, there is a risk of creating a sequential monotherapy-like approach. I think the best chance for resuppressing the virus to less than 50 copies/mL is to replace 2 drugs.

**Dr Lane:** We do not know the CD4+ cell count for this patient. Given her age, if she has a relatively high CD4+ cell count, you could make the case for waiting and watching. Even though it may be difficult to resuppress the viral load, protease inhibitors are still an option.

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#### Case 4

*A 22-year-old woman has been on antiretroviral therapy for approximately 5 years. Her current CD4+ count is 290 cells/ $\mu$ L and her plasma HIV-1 RNA level is 54,000 copies/mL. She has taken every antiretroviral drug available, and has been on and off therapy at various times. Her current regimen is didanosine/zidovudine/efavirenz. Genotypic testing shows major reverse transcriptase mutations at positions 41, 215, and 103 and protease inhibitor mutations at 46, 90, and 84. Would you order phenotypic testing, use lamivudine in the next regimen since there was no M184V mutation, or use tenofovir in the next regimen?*

**Dr del Rio:** This is a complex genotype that is hard to interpret. A phenotype may help, but even if the M184V mutation is not present in a patient who is not currently taking lamivudine, the mutation may surface when he or she starts lamivudine again.

**Dr Lennox:** Findings from a recent study by Parkin and colleagues showed that for some drugs there is a sizable discordance between phenotype and genotype. This was observed in the laboratory, and the clinical utility of these findings is not clear. In this patient, it may be useful to order phenotypic testing to determine if there are drugs that by genotype appear to be ineffective, but by phenotype may be useful.

**Audience Comment:** The issue of ordering a phenotype for this patient is the same as that of ordering a genotype: the patient currently is not taking all of the drugs to which her virus has been previously exposed. Can you really obtain useful information from a drug resistance assay if she is currently taking only didanosine, zidovudine, and efavirenz?

**Dr Lennox:** The utility and reliability of phenotypic or genotypic testing results are not clear in this setting.

**Dr Johnson:** Ideally, resistance test results would reflect the archival history of drug exposure, not just the current exposure. It is difficult to sort out discordance between genotype and phenotype by drug because patients may have numerous mutations; we do not fully understand the net clinical effect of a given set of resistance mutations. In the “old days,” virus with lamivudine resistance mutations could become resensitized to zidovudine. Now, for example, if 3 or more nRTI-associated mutations and the M184V mutation are present in virus, there may be dual resistance.

**Audience Comment:** The issue with this case may not be a biochemical one. When you see drug failure like this, your first, second, third, and fourth thoughts should be about adherence. Only after exploring potential adherence problems should you discuss a new regimen.

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#### Case 5

*A 31-year-old man with HIV infection is seropositive for hepatitis C virus (HCV) infection. His CD4+ count is 118 cells/ $\mu$ L and his plasma HIV-1 RNA level is 76,000 copies/mL. He is taking trimethoprim-sulfamethoxazole for PCP prophylaxis. After 10 weeks of zidovudine/lamivudine/abacavir, his aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels have increased from 65 and 80 U/L to 185 and 250 U/L, respectively. The total bilirubin and albumin levels are normal. He reports no use of alcohol, dietary supplements, or any other medications that may be increasing his AST and ALT levels. Would you recommend stopping antiretroviral therapy, or continuing antiretroviral therapy and adding interferon alfa and ribavirin?*

**Dr Sulkowski:** When a patient develops hepatitis, defined as an increase in liver enzymes suggesting increased hepatocellular necrosis, the first step is to generate differential diagnoses. Hepatitis A virus and hepatitis B virus are also very common. If these tests are negative, then you should suspect the antiretroviral therapy as the cause of the hepatitis.

Data from the Swiss Cohort Study show that approximately 60% of patients who developed a grade 3 or 4 toxicity and continued to take the same regimen did not experience an adverse outcome. This finding has been supported by results of other cohort studies; many patients have favorable outcomes with observation only. One argument in favor of continuing the regimen would be that the zidovudine/lamivudine/abacavir regimen has been associated with a relatively low rate of hepatotoxicity of any combination antiretroviral therapy regimen.

**Dr Gulick:** What about the immune reconstitution syndrome with concomitant HCV infection?

**Dr Sulkowski:** Immune reconstitution syndrome refers to the observation that after starting antiretroviral therapy, there may be a specific anti-HCV immune reaction leading to increased hepatocellular cytolysis. There are no data firmly supporting this effect. Some data indicate that the HCV viral load increases after initiation of HAART, suggesting that liver cells are being destroyed. However, there are no studies that show specific cytotoxic T-cell immunity to HCV in the liver, so the immune reconstitution syndrome in HCV infection remains an unproven hypothesis.

**Dr Gulick:** How would you otherwise account for the increase in HCV levels in the blood?

**Dr Sulkowski:** The reason for increased levels of HCV is not clear. In the case of cytomegalovirus (CMV), for example, the CMV viral load decreases with initiation of antiretroviral therapy. Research shows that an HIV-seropositive patient population has a higher HCV viral load than an HIV-seronegative population, so you would expect that if you added HAART and improved immune system function, the HCV viral load would decrease. We do not yet understand the effect, in part because studies that incorporate liver biopsies before and after the initiation of antiretroviral therapy have not been conducted. There is some evidence to suggest that immune cells in the liver may be different than those found in the peripheral blood.

**Dr Lennox:** There is controversy over whether measuring levels of HCV RNA predicts tissue damage in the liver.

**Dr Sulkowski:** Indeed, there are no studies that show that HCV viral load in the blood correlates with hepatic inflammatory activity, ALT levels, or fibrosis. In HIV disease, HCV viral load is not a good marker of disease progression. Liver biopsy may be helpful, but often we do not have biopsy results in this kind of clinical scenario.

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## Case 6

*A 32-year-old woman was diagnosed with HIV infection in 1995. At that time, her CD4+ count was 520 cells/ $\mu$ L and her plasma HIV-1 RNA level was approximately 11,000 copies/mL. She began taking stavudine/lamivudine/indinavir and has had 1 episode of nephrolithiasis (successfully treated). For the last 4 years, her plasma HIV-1 RNA level has been less than 50 copies/mL. Her current CD4+ count is 840 cells/ $\mu$ L. She has heard about the long-term complications of HAART and is concerned. Do you maintain the current regimen, substitute a drug for indinavir, substitute zidovudine for stavudine, replace both indinavir and stavudine, or stop her current therapy and observe?*

**Dr Thompson:** This patient began therapy in 1995 with a CD4+ cell count and plasma HIV-1 RNA level that would have indicat-

ed deferral of therapy under current treatment guidelines. I might consider stopping therapy because I am concerned about the long-term adverse effects of antiretroviral therapy in such patients. If we stop therapy, we may be able to spare this patient several years of therapy, but we would have to monitor the CD4+ cell count very, very closely. Her CD4+ cell count is 840/ $\mu$ L now, but it could decline rapidly if she stops therapy. It would be ideal to enroll this patient in a clinical trial.

**Dr Hadigan:** The first thing that I would recommend is checking her cholesterol, lipid, glucose, and insulin levels, as well as her body shape and appearance. It is also important to ask if she has noticed physical changes or has specific concerns. There are some data that suggest that if a patient has been on this regimen for this length of time and has not developed any problems, it is unlikely that he or she will do so in the future. If she has tolerated this combination for several years and has a fasting cholesterol level less than 200 mg/dL, a low-density lipoprotein cholesterol level of less than 160 mg/dL, a reasonable triglyceride level (<300 mg/dL), and has not experienced any significant changes in body fat distribution, I would recommend that she stay on this regimen. Some patients tolerate regimens very well for periods of 5 or more years.

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## Case 7

*A 20-year-old woman was found to be HIV-seropositive during a prenatal work-up. Her CD4+ count was 540 cells/ $\mu$ L and her plasma HIV-1 RNA level was 12,000 copies/mL. She started zidovudine, lamivudine, and nevirapine and had a genotype indicating wild-type virus. Her plasma HIV-1 RNA level was less than 50 copies/mL at delivery, and she gave birth to a healthy, HIV-seronegative baby. She presents 2 months later and does not have a strong opinion about continuing antiretroviral therapy or not. She is not breastfeeding. Would you recommend continuing or stopping therapy?*

**Dr Treisman:** I would suggest stopping therapy. It is important to explore other issues that for individual patients may have a more profound impact on treatment decisions than CD4+ cell counts or viral load. For example, this woman does not have a strong opinion about antiretroviral therapy. Does she have a long-term partner? Does having an undetectable viral load mitigate her concerns about transmission? Does she have concerns about the drugs that are coloring her opinion?

**Dr del Rio:** Data have shown that pregnant women adhere to antiretroviral therapy regimens very successfully during pregnancy, but that severe adherence problems begin after delivery. Two of the drugs this woman is taking are lamivudine and nevirapine, to which she could develop resistance very rapidly. If the recommendation is to continue therapy, it is essential to work on adherence.

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