

CASE PRESENTATIONS AND DISCUSSIONS

On July 1, 1998, the updated recommendations of the International AIDS Society–USA Antiretroviral Therapy panel were published in the *Journal of the American Medical Association (JAMA)*. This third report of the panel, which was initially convened in 1995, reflects the continued understanding of HIV pathogenesis and its treatment.

Currently available potent antiretroviral therapy has been remarkably effective in improving the quality of life and preventing disease progression in a large proportion of individuals in areas of the world in which the drugs are available. However, the approach to effective antiretroviral therapy continues to evolve rapidly. Newly available antiretroviral drugs, current data about the relative effectiveness of various combinations of drugs, recognition of unanticipated long-term complications of potent therapy, new data suggesting that eradication of HIV is unlikely after 2 years of potent antiretroviral therapy, and the emerging role of more sensitive HIV RNA assays warranted an update of the panel's recommendations. In addition, the IAS–USA panel on HIV resistance testing released its first report on the clinical potential as well as current limitations of HIV resistance testing for individual patient management. That paper was published in *JAMA* on June 24, 1998.

In order to support the clinician and patient in dealing with current therapeutic challenges, the International AIDS Society–USA held a symposium on Antiretroviral Therapy on July 1, 1998, at the 12th World AIDS conference in Geneva. Members of the two panels discussed possible therapeutic approaches for difficult clinical scenarios. The panel's discussions of the specific cases herein are intended to illustrate the principles of therapy, rather than to dictate a single approach to a particular situation. The discussions focus in large part on the role of currently available drugs. However, the possible roles of newer, investigational drugs, particularly those that are available through expanded access programs were also discussed.

Effective antiretroviral therapy requires the full understanding of, and commitment to, the regimen, and is dependent on close interaction between the patient and the physician in developing a regimen that is appropriate to the individual patient. In many scenarios, especially in antiretroviral-naïve patients with early HIV disease, there is a great deal of flexibility in determining when to initiate treatment, and what regimen would be most appropriate to achieve a durable response. Although therapeutic options are less flexible for patients with considerable previous experience with antiretroviral drugs, close patient/physician interaction is just as essential.

It is important to note that the symposium took place in July, and the optimal approach to antiretroviral therapy has evolved further still since that time. This summary attempts to include this new information, but it is important for clinicians to monitor the new insights in this field, as they affect therapeutic decisions.

SECTION I: CLINICAL ASPECTS OF HIV RESISTANCE TESTING

CASE 1

DR JOHNSON: This is a patient who began an initial regimen of zidovudine, didanosine, and indinavir. After 4 months, the plasma viral load was below 50 copies/mL. Subsequent measurements are as follows:

Month	Plasma HIV RNA (copies/mL)
6	200
7	<50
8	350
9	<50

What would you recommend for this patient?

DR CONWAY: This is a situation that reflects what many of us are seeing as the more sensitive plasma viral load assays are being used more widely in clinical practice. It is now quite clear that having levels below the level of detection, even with these more sensitive tests available, does not represent elimination of the virus from the body. In fact, it may well not represent elimination of the virus from the plasma. In this context, the difference between a value below detection and measures of 200 or 350 copies/mL may not represent a fundamental change in efficacy of the regimen. It may simply reflect a mild alteration of the balance between the host, the drugs, and the virus, at least temporarily, favoring the virus. Data from Havlir et al and Mayers et al (among others) suggest that most of these early virologic breakthroughs are not generally associated with the emergence of viral resistance and do not necessarily imply that the regimen has failed.

In this case, a review of the regimen and its components is

definitely in order. The combination of didanosine and indinavir requires five fasting (or near-fasting) states a day. Administering the didanosine once daily may improve adherence to the regimen and enhance its efficacy. A review of the dietary requirements to optimize indinavir absorption may also help. At some point in the future, individualizing the indinavir dose based on blood levels may be indicated, if this is shown to be clinically useful in ongoing studies.

In my opinion, intensifying the regimen by adding another active drug would carry unacceptable risks of additional toxicity

and the limitations of future therapeutic options if the more complex regimen were to fail. A lower-risk intervention may be the addition of hydroxyurea to enhance the potency of the didanosine, although even this should be done cautiously in light of the synergistic hematologic toxicity of zidovudine and hydroxyurea.

This case makes the point that all virologic breakthroughs are not created equal. Management must be individualized, based on the particular regimen, available options (including strategies to enhance adherence), and the specific repeated measures of plasma viral load.

CASE 2

DR JOHNSON: This patient presented with primary HIV infection in September 1997. ELISA testing was positive; plasma HIV RNA level was 9,000,000 copies/mL; and Western blot showed a p24 band. The patient began taking a regimen of stavudine/lamivudine/indinavir. Genotyping of the RT gene (sample taken September 1997) showed the following mutations: T215Y and M184V. The protease gene had M46L and V82A. The plasma viral load data are as follows:

Date	Plasma HIV RNA (copies/mL)
9/97	9,000,000
10/97	11,000
12/97	1600
2/98	5000

What do you recommend for this patient?

DR BRUN-VÉZINET: This is a case in which the primary HIV infection was identified very early; the HIV RNA load level was high and Western blot showed only antibody to HIV p24. The therapy was initiated early with a potent antiretroviral regimen containing a protease inhibitor, which is consistent with current recommendations. In this setting, the viral load can be expected to decline below 200 copies/mL by month 3 or month 4. In this

patient, the therapy has failed, evidenced by the viral load levels at months 3 and 5. Therapeutic failure might result from poor adherence, as adherence is a crucial factor for achieving maximum reduction of the viral load. However, in this patient, the therapeutic failure is clearly due to infection with a virus that was already resistant to 2 of the components of the potent drug regimen. This situation must be increasingly suspected in early-treated seroconverters if the plasma viral load is not below 200 copies/mL by month 3, or not below 50 copies/mL by month 5 or 6. In this patient, changing therapy is indicated.

DR JOHNSON: An important question is how common is multi-drug-resistant HIV in primary HIV infection?

DR KURITZKES: There is now evidence from the seroprevalence surveys from Geneva, and from the data accumulating in the United States, that up to 7% to 10% of virus isolates have resistance mutations for the NRTIs, and somewhere between 5% and 7% have mutations associated with resistance to protease inhibitors. This is beginning to support the consideration of more routine testing of patients with primary infection. If resistance testing is done, the very first available sample from the patient should be used. The longer after transmission of the isolate the testing is done, the greater the chance that a wild-type revertant might have overgrown, leading to a situation where resistant virus, lurking as latent provirus DNA in the infected cells, may not be detected. Clearly, more organized collaborative surveillance studies among all patients who are identified with primary infection are needed to establish the incidence of primary resistance in different geographic regions.

CASE 3

DR JOHNSON: This patient has a history of successive antiretroviral therapy:

1989 – 1992 zidovudine
 1993 didanosine
 1994 zidovudine/didanosine
 1995 zidovudine/lamivudine
 March 1996 stavudine/lamivudine/ritonavir

The known viral load and CD4+ count history is as follows:

Date	Plasma HIV RNA (copies/mL)	CD4+ count (cells/ μ L)
3/96	80,000	88
8/96	5800	184
3/97	92,000	200
Antiretroviral regimen changed to stavudine/lamivudine/ritonavir/saquinavir		
5/97	18,000	230
11/97	15,000	260
2/98	30,000	310
5/98	70,000	180

A change to a regimen with at least 2 new drugs will be made. The patient's virus was sent for phenotypic analysis (5/98) to evaluate possible drug options. The results for analysis of the reverse transcriptase inhibitors are as follows:

Drug	IC ₅₀ results
Zidovudine	<4-fold S
Lamivudine	>10-fold R
Didanosine	<4-fold S
Stavudine	<4-fold S
Zalcitabine	<4-fold S
Nevirapine	<4-fold S
Delavirdine	<4-fold S
Abacavir*	<4-fold S
Efavirenz	<4-fold S

* experimental drugs at this time; R indicates resistant, S indicates susceptible

CASE 3 (continued)

The isolate also showed high-level resistance (>10-fold increase in IC₅₀) to all four approved protease inhibitors, as well as to several investigational drugs in this class.

This case gives rise to several questions: What is the role of phenotyping in salvage decisions? What is the likelihood that these isolates will respond to the nonnucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitors? What is the role of viral genotypic and phenotypic testing in predicting subsequent viral load response?

DR MELLORS: This is a good example where susceptibility testing might help to identify the cause of treatment failure. This patient has a high plasma viral load and a CD4+ cell count of 180 cells/ μ L, and is taking antiretroviral therapy. Resistance to the approved and experimental protease inhibitors has been identified, making poor adherence an unlikely cause of the persistent plasma viremia. One option is to wait for several new drugs to become available and change the entire regimen. But I do not think this patient can wait, so I would try to put together a regimen from available options.

Although the virus appears to be susceptible to zidovudine, the prolonged history of prior zidovudine use argues against its use now as recycling might allow emergence of a resistant mutant very quickly. The treatment history and susceptibility testing suggest that the current options include didanosine, stavudine, zalcitabine, perhaps the experimental drug abacavir, and an NNRTI. However, this patient has taken didanosine and stavudine in the past and it is not known if resistance to these compounds has developed and is now latent. Viral resistance to stavudine may not necessarily be associated with phenotypic resistance. We would expect that this patient will respond to an NNRTI (perhaps efavirenz), but unless that is partnered with additional potent agents, we would expect resistant mutants to emerge rapidly. Unfortunately, potential partners are few. Abacavir could be an option. There are data with nRTIs and protease inhibitors that show that the baseline phenotype is predictive of response, particularly with abacavir. If there is a greater than 8-

fold increase in the IC_{50} to abacavir, the likelihood of response is extremely low. The likelihood is greater with virus that is sensitive (<4 -fold increase in IC_{50}). Although we can expect a response to an NNRTI, or to abacavir, it may not be sufficient in this pa-

tient with advanced-stage disease to produce sustained reduction of viremia. Possible other drugs to add are the experimental agent adefovir, or didanosine and hydroxyurea.

CASE 4

DR JOHNSON: This next case is a 36-year-old woman who has been taking zidovudine/didanosine for 5 years. She had a good initial clinical and CD4+ cell count response. Recently, the CD4+ cell count fell from 200 to 50/ μ L and the plasma HIV RNA rose from 10,000 to 100,000 copies/mL.

Recent genotyping of virus reverse transcriptase showed the following mutations: V75I, F77L, F116Y, Q151M.

What do you recommend for this patient?

DR CLOTTET: The genotypic analysis tells us that this patient harbors a multidrug resistant strain of HIV: two mutations observed in this case confer reduced sensitivity to multiple RT inhibitors. The multidrug resistant strains have been reported primarily among patients who were taking zidovudine and didanosine, and among patients who were taking zidovudine/didanosine and then zalcitabine. There are anecdotal reports of multidrug-

resistant strains in patients who have taken stavudine/hydroxyurea/didanosine. It is important to recognize that currently available genotyping methods (the line-probe assay; LiPA) will not detect this mutation. However, there are experimental LiPA assays and selective PCR methods that may be very useful for evaluating expression of these mutations.

The therapeutic approach that could be recommended would include 2 protease inhibitors and 1 NNRTI (nevirapine or perhaps efavirenz). According to the local availability of drugs in different countries, we might add adefovir or perhaps hydroxyurea plus didanosine because studies show that hydroxyurea may boost didanosine activity in spite of the presence of the 151 mutation. We have recently reported that the prevalence of the multidrug-resistant mutation in Spain is 2.7% and has not changed since 1993. Thus, the prevalence of this mutation in our country does not support the need for testing for it prior to changing therapy, except in special cases.

DR LOVEDAY: There are data available for other regions of the world as well. The ENVA (a European network for quality assurance of molecular virology assays and clinical trials) group defined a 2% prevalence of 151 mutation, and our group from the Royal Free Hospital in London defined prevalence at 1.6%. It is a bad mutation, but it does not yet appear to be very prevalent.

SECTION II: INITIAL ANTIRETROVIRAL THERAPY: WHEN TO START AND INITIAL REGIMENS

CASE 5

DR FISCHL: This case details a 25-year-old man who has been known to be HIV seropositive for about 1 year. The CD4+ and plasma HIV RNA levels are measured for the first time:

- * CD4+ cell count is 720/ μ L
- * HIV RNA level is 1100 copies/mL

What are your treatment recommendations for the patient?

DR VOLBERDING: The first step with this patient is to confirm the presence of HIV infection, as well as the initial laboratory values. The HIV RNA level is low enough that it is in the range of false-positive results, and the HIV RNA assays are not designed to be diagnostic tests. Once HIV infection, CD4+ cell count, and HIV RNA values are confirmed, the potential risks and benefits of therapy can be discussed. Obviously, we want to initiate therapy be-

fore serious or irreversible immunologic damage occurs. However, starting therapy too soon has risks in terms of nonadherence, viral breakthrough, or viral resistance at a point where the patient is still very early in the course of disease. We have also learned in the past couple of years that starting therapy too soon in patients who have not themselves really made the commitment to the rigors of the regimens is a mistake.

The decision hinges on the patient's wishes at this point. That being said, I think he does not yet need to start therapy, because his viral load is very low, CD4+ count is within the normal range, and he has, at this point, a low risk of serious complications from this infection. I think that it is not wrong to recommend treatment for somebody with very early disease, but in my opinion this patient should be advised to defer therapy. He should be monitored closely.

DR MELLORS: I would add that we need to consider whether this patient has other than a clade B type virus, if he is not from the US, because the plasma viral load assays will give a falsely low HIV RNA result in patients who have non-clade B virus.

CASE 6

DR FISCHL: This case involves a 21-year-old model who is diagnosed with HIV infection and found to have a CD4+ cell count of 350/ μ L and an HIV RNA level of 35,000 copies/mL.

The patient is interested in beginning therapy but has expressed concerns about the peripheral fat redistribution syndromes developing in people taking protease inhibitors. What are your recommendations for the patient?

DR MONTANER: This patient has a CD4+ count of 350 cells/ μ L, a viral load of 35,000 copies/mL, and discussion should be initiated about therapy and treatment options should be carefully reviewed with the patient based on the data that we have available. There is a growing body of data that support a variety of potent regimens, including data from studies such as the AVANTI II, III, and INCAS

trials, as well as those including efavirenz, abacavir, and saquinavir soft-gel capsules. In these trials, about 50% of the patients have a viral load that declines below the limit of detection using the most sensitive assays available and around 70% or so below the 400 or 500 copies/mL limit. So I think that what we need is to sit down with the patient, carefully discuss the options, the safety, the commitment, the type of adherence requirements, and then based on that, the patient should make a choice. In this patient, a protease inhibitor-sparing regimen may be appropriate because of the concerns that were expressed. In the absence of comparative data, the 3 NNRTIs currently available (nevirapine, delavirdine, and efavirenz) are each regarded as a viable option as components of a triple-drug regimen, with the specific choice to be based on the individual clinical situation and patient preference.

DR THOMPSON: I agree that we need to take the risk for lipodystrophy seriously. We need to talk with the patient about the possibility that they may develop lipodystrophy even on a non-protease inhibitor-containing regimen. The data are only anecdotal at this point, but there appear to be several cases of lipodystrophy occurring among patients who are taking potent regimens that contain NNRTIs.

DR KATZENSTEIN: Another potential regimen to consider in this setting is a triple-nRTI combination. If the data that Dr Fischl presented (eg, zidovudine/lamivudine/abacavir) are

confirmed in longer follow-up, then it may provide for yet another alternative.

CASE 7

DR FISCHL: A 32-year-old man presents with PCP and is found to be HIV seropositive. After treatment for PCP is completed, his CD4+ cell count is 30/ μ L, and his HIV RNA level is 150,000 copies/mL.

What are your recommendations for the patient?

DR KATZENSTEIN: This is an instance where we clearly have someone who needs aggressive therapy. Unfortunately, we do not have good data on the comparative potencies of different initial regimens in advanced-stage patients (ie, very high viral load and CD4+ counts below 50 copies/ μ L) who are naive to therapy. These are a group of patients where we want to exert the most potency, and I would most likely recommend a dual protease inhibitor regimen with 2 potent nRTIs. The question is whether more patients who have high HIV RNA levels should take an NNRTI, and we are just beginning to get those answers. In 1 study, efavirenz and indinavir had similar potency. An NNRTI, a protease inhibitor, and 2 nRTIs might be a consideration to be brought to the fore. This is where discussion with the patient about the need to follow through with each of these therapies is critical. It's our role as physicians to really stress the importance of this with him and understand his commitment.

DR VOLBERDING: We have seen more data on the use of hydroxyurea and didanosine at this meeting and I wonder whether we can consider that as part of initial therapy. We have tended to think of it more as salvage therapy; would anyone recommend this for a case like this?

DR MONTANER: Dr. Lupo and colleagues presented data from a study of hydroxyurea as part of an initial regimen. Basically, the antiviral response was enhanced, and the absolute CD4+ response was dampened. However, the CD4+ percentage response is actually not dampened. I do think it is a consideration, but its effect on the absolute CD4+ count may be a bit problematic for this patient.

The other issue is whether or not patients with higher plasma viral load levels require more aggressive therapy and the answer is that we do not know. In analyses of various studies, there is a consistent trend toward a decreased response as the pretreatment viral load increases, and so one is tempted to assume that adding more treatment may help. But adherence is the major problem, so this is a difficult question and we need objective data.

Finally, we have seen good data regarding the effectiveness of triple drug therapy that includes an NNRTI (Dr Vella's group with nevirapine and Dr Staszewski's group with efavirenz, for example) in the context of initial therapy for patients with high viral loads.

DR MELLORS: Personally, without controlled trial data on the use of hydroxyurea in advanced disease with low CD4+ cell counts, I would not be inclined to recommend it.

DR HAMMER: It is clear that there are different options for what one might initially choose. This case illustrates the importance of early and intensive monitoring of the therapy. The early virologic response is an important predictor of a durable response. Specifically, assessing the viral load at the 4- and 8-week marks will help you to know if the regimen is successful, or if it might need to be changed, or even if intensification of the regimen might be considered.

SECTION III: CHANGING ANTIRETROVIRAL THERAPY: WHEN TO CHANGE AND WHAT TO CHANGE TO

CASE 8

DR VELLA: This patient had a baseline CD4+ count of 250 cells/ μ L and plasma HIV RNA level of 30,000 copies/mL and began stavudine/didanosine/nelfinavir. The plasma HIV RNA was <400 copies/mL for about 1 year. 3 months later;

- plasma HIV RNA is 3000 copies/mL
- CD4+ count is 400 cells/ μ L

Adherence has been good.

What would the panel recommend for this patient's antiretroviral therapy? Following are some possible strategies to consider:

1. No change
2. Change all elements of the regimen, keeping within the nRTIs and protease inhibitor classes of drugs (eg, zidovudine/lamivudine/ritonavir/saquinavir)
3. Change all elements, including the addition of an NNRTI (eg, zidovudine/lamivudine/indinavir/efavirenz)
4. Change the nRTIs, discontinue the protease inhibitor, and add an NNRTI (eg, zidovudine/lamivudine/efavirenz)

DR BRUN-VÉZINET: The first step before considering a change in the regimen is to confirm the rebound of the viral load. A repeat test should be performed on a specimen collected at least 1 week later. Once the rebound is confirmed, the first option to consider is no change. From the virologic point of view, I think that this is not the preferred approach. Continuing with this regimen and with the ongoing virologic replication will be associated with accumulation of mutations that select for resistance and particularly for mutations in the protease gene. This could ultimately preclude the use of any other protease inhibitor.

In my opinion, changing therapy is indicated for this patient. But, with 3 requirements: first, we need to change the drug

regimen in its entirety; second, we should have a second line regimen as potent as the first; and third, we need to select alternative drugs that have low potentials for cross-resistance with the drugs in the initial regimen.

My recommendation is the second approach: switch to 2 new nRTIs and 2 new protease inhibitors. The choice of new nRTIs (among the approved drugs in the class) in the patients on stavudine and didanosine is limited. I would change the nRTIs to zidovudine and lamivudine. Nelfinavir selects mainly for resistant mutants with 1 mutation at codon 30, and this mutant is likely to be susceptible to ritonavir and saquinavir, so I would recommend this dual protease inhibitor combination.

DR THOMPSON: I would likely recommend changing the regimen as well. One thought that comes to mind is the idea of intensification with something like hydroxyurea or hydroxyurea and adefovir, for example. Clearly there are no supportive data, but I think it's an interesting idea, using something that is not going to put the patient at risk for blowing a whole new class of drugs. For example, intensifying the regimen with an NNRTI, or using just 1 drug where the resistance profile leads us to believe that we would lose that drug and maybe others would make me nervous. However, if we did not get an adequate response fairly quickly, I would change aggressively.

DR MONTANER: My recommendation in this case would be to change to stavudine/didanosine/ritonavir/saquinavir and hydroxyurea.

DR KURITZKES: I would tend to agree. If you are going to hold out for a little bit, it would be important to discontinue the protease inhibitor. You don't want the continued pressure of the nelfinavir, which might allow for the selection of broader cross-resistance with further limitations on the options even further down the line.

DR VELLA: Clearly there are several possible options in this setting because it is a situation where the drug failure is identified early, and the patient does not have very advanced disease and is adherent, so we know it is a patient who might be able to follow a number of different recommendations.

CASE 9

DR VELLA: This next case is a patient who began therapy with zidovudine/lamivudine. At 18 months, the CD4+ count was 150 cells/ μ L and indinavir was added to the regimen. One year later, the plasma HIV RNA rose from 3000 (nadir) to 30,000 copies/mL; the CD4+ cell count was stable at 300/ μ L. The antiretroviral regimen was changed to stavudine/didanosine/ritonavir/saquinavir, which gave a transient 1-log drop in HIV RNA over the next 3 months. Nine months after the switch, the HIV RNA level is 60,000 copies/mL and the CD4+ count continues to remain stable at 300 cells/ μ L.

The patient's adherence is good. What is going on?

DR MONTANER: Obviously this is a difficult case that brings up the question of discordant responses. However, looking back at the history of antiretroviral therapy, particularly with dual nucleosides, this has always been an issue. For example, in the ACTG 175 and DELTA studies, early rebound in viral load was associated with a delayed CD4+ count decrease. The lag time was even longer if clinical events are considered. I suspect, although it has not yet been demonstrated, that what we are seeing with triple therapy regimens is a magnification of this effect. My prediction is that in due course, these patients will have declines in the CD4+ counts. In the meantime, that does not mean that they have not been protected. Of course they have been.

DR VELLA: What would the panel recommend for this patient? Some options might include:

1. No change
2. Intensify current therapy: eg, add hydroxyurea and/or NNRTI
3. Change to new drugs/classes
 - without nRTI recycling: eg, didanosine/hydroxyurea/NNRTI/protease inhibitor
 - with nRTI recycling: eg, zidovudine/lamivudine plus didanosine/hydroxyurea/NNRTI/protease inhibitor
4. Interrupt therapy

DR KATZENSTEIN: There is no question that protease inhibitors are gone as an option. Resistance testing of the reverse transcriptase of this patient might be considered, because all of our clinical experience tells us that we are no longer benefiting the patient with the protease inhibitors. His viral load is increased and given that he has taken 3 protease inhibitors over the past 1 1/2 years to 2 years, we are unlikely to have any effective protease inhibitor. I would suggest we change to multiple drugs including hydroxyurea and didanosine, as well as perhaps adefovir. Hopefully soon we will have other nRTIs available so I would change all classes of drugs, but I don't see a reason to change to a new protease inhibitor; it should be discontinued.

I agree that the discordancy that we are seeing is one that we can feel some ease with respect to the patient's immediate risk of progression, but I do have concern about his long-term prognosis raised by the rising plasma virus load.

DR VELLA: How might the recommendations change in this case, if the CD4+ cell count were low (ie, about 80 cells/ μ L)?

DR KURITZKES: The difference here with this patient is that the CD4+ count has dropped to 80 cells/ μ L along with the rise in HIV RNA. Something different clearly needs to be done, but exactly what to do is a much more difficult question. I am again tempted to move to the addition of hydroxyurea with an NNRTI with perhaps also adefovir if it were available, because in this patient, protease inhibitors are most likely exhausted as an option. If clinical trials were within reach, then the possibility of enrollment in a study of one of the "second generation" protease inhibitors could be considered or some of the other studies in antiretroviral experienced patients that are planned or under way. I would be concerned about the use of zidovudine in a regimen that includes hydroxyurea because of likely synergistic bone marrow toxicity. There are really no data about adding a second NNRTI so my recommendation would be to try didanosine/hydroxyurea/an NNRTI and adefovir, if it were available.

DR SAAG: I would add an important note regarding the use of adefovir. Some data were presented at this meeting demonstrating a significant increase in the antiretroviral activity of adefovir against clinical isolates containing an M184V mutation. Specifically, the use of adefovir in patients harboring virus without the M184V mutation results in about a 0.4- to 0.6-log reduction in viral load. When used in patients who have M184V mutant viruses, the level of activity was on the order of 0.8- to 1.0-log

decrease in viral load. So one consideration is to try to keep lamivudine or abacavir as part of an adefovir-containing regimen.

DR YENI: I think that the largest difference between the situation (stable CD4+ cell count of 300/ μ L) and the one in which the CD4+ cell count has declined to 80/ μ L is not so much in the type of drugs that one is going to choose for the subsequent regimen

but with the amount of time one has in which to make the decision. In the first situation, there is some time to make this decision because the CD4+ count is high. So it might be acceptable to wait a little bit until several more new drugs are available. In the second case, however, the change needs to be made right away because the CD4+ cell count is at a more critically low level.