although 6 never received any doses of adefovir. Therefore, out of the 56 patients receiving adefovir, 11 of these 56, or 20 percent, were permanently discontinued, 5 for deaths unrelated to this drug; 4 moved from the area; and 2 did have severe toxicities on the 120 mg dose. Thirty-six of the 56 patients, or 64 percent, have had either their Preveon held or their antiretrovirals on hold. Eleven of the patients, 20 percent of this total, are on hold due to side effects and may not start the drug again. Twenty-two patients, or 39 percent of the total, have had nephrotoxicity by lab criteria and, hopefully, will await resolution and restart the drug in the near future. Three patients have stopped the drug due to other complicating illnesses. Nine patients currently remain on study, 10 percent of the 56 patients, and are still on therapy as a salvage regimen.

The salvage regimen, as a backbone, had abacavir, aprenavir, either D4T AZT, and all were on 3TC. They range anywhere from 4 weeks to 68 weeks on therapy. All of these 9 patients have had a greater than 1 log drop in viral load, and 2 out of the 9, or 22 percent of the patients, have viral loads of less than 50 copies by the bDNA assay. One patient has been on treatment now for 68 weeks. It is of note, however, that 5 of the 9 patients are now on therapy with the 30 mg a day dose, and appear to have sustained

undetectable viral load.

With regards to the side effects and toxicities, you heard about them earlier. They seem to be reasonably tolerated. The nephrotoxicity was extensively discussed. It is easily identifiable through meticulous monitoring, and is usually amenable to electrolyte replacement and/or dose reduction of adefovir. It is my hope that many of these patients will also be able to resume their adefovir once their laboratory parameters improve.

So, in summary, based upon the accelerated approval criteria presented this morning by Dr. Jolson, I encourage this committee to approve adefovir based upon the following:

Number one, it offers convenient once a day dosing in general, and is well tolerated with some mild side effects.

Number two, it has a different toxicity profile than the currently available antiretrovirals, with nephrotoxicity as the AE being easily identified, managed, and appears to be largely reversible.

Number three, for many patients who have already failed multiple antiretroviral regimens, it may provide them with a unique resistance profile to combine with other antiretroviral agents. Even if these patients only get 6-12 months of benefit from this drug, it may, in fact, bridge

the gap for many patients until the next wave of antiretroviral drugs become available, presumably effective against multi-drug resistant HIV.

Finally, something that has not been discussed today is that adefovir may provide additional antiretroviral benefits against other viruses commonly co-infecting HIV, including hepatitis B and CMV. Thank you.

DR. HAMMER: Thank you very much. The next speaker is Dr. Charles Farthing.

DR. FARTHING: Good afternoon, Mr. Chairman. My name is Charles Farthing. I am a Board certified ID physician. I am medical director of AIDS Healthcare Foundation in Los Angeles, and a clinical assistant professor of medicine at UCLA. I have been an investigator on several adefovir studies, and on the HIV advisory board for Gilead. I did receive travel support to come to DC today, but I didn't want to come to DC today.

[Laughter]

At AIDS Healthcare Foundation we care for some 4000 HIV patients, and I supervise some 16 primary care providers, and we have had about 130 patients on expanded access with adefovir.

At the beginning of today's proceedings we were told there were two reasons why a drug might receive accelerated approval. One is it is more potent than other

agents. That clearly does not apply to adefovir. The other was that it works when HIV is resistant to other medications, and this, in my mind, does constitute a reason for approval of this drug. In my interpretation of the data, adefovir definitely does have a unique resistance profile.

As a clinician, I am concerned that there are many patients now highly resistant to nucleosides and PIs, and many of these patients may not survive the probable two years until other agents, such as DPC961, AG1574, tenofovir and AG17176, that will hopefully salvage them, become available.

Also, many of our currently failing patients are highly nucleoside and PI exposed but still NNRTI naive, and I feel we need to protect that NNRTI and using adefovir as part of a cocktail is one way that we may be able to do that, and these are the ways that I am currently using adefovir in the clinic.

In two years the need for adefovir in HIV treatment may not be great as we will by then probably have the new drugs I have mentioned. Also, we will probably have tenofovir which seems likely to fulfill its promise of being a better than adefovir with the same favorable resistance profile, three times the potency and, hopefully, without the nephrotoxicity but this is at least two years away.

Therefore, the need for adefovir is now, not later, and I would ask the committee not to delay approval. It would be sad if you delayed approval and then approved the drug in two years time perhaps when we may not need it.

Leaving it just on expanded access is not a very good option in my mind either as many cannot access expanded access programs, and even in sites where expanded access programs are running the physician may well choose not to use it just because of the extra work and hassle it involves for him to provide it for the patient.

Finally, I would like to add that we didn't find toxicity management particularly difficult with our 130 patients on expanded access. We had no serious nephrotoxicity leading to dialysis, and I found it reasonably easy to instruct our 16 providers on how to monitor their patients, supplement their patients and discontinue when necessary. Thank you.

DR. HAMMER: Thank you very much. Dr. Howard Grossman?

DR. GROSSMAN: I am an internist from Manhattan and like Dr. Jones, I am on staff at St. Luke's Roosevelt Hospital and an assistant clinical professor of medicine at Columbia. I am here also to speak in favor of approval for adefovir dipivoxil. I did get transportation support. I am an investigator on the ATHART trial, the GS415 trial that

was described earlier, the intensification trial, and we have extensive experience with expanded access.

My clinic employs three doctors and a physician's assistant. We follow a little over 700 patients at this time. We are running about 22 clinical trials, mostly Phase III and IV pharmaceutical-sponsored trials, and we also have our own trials that we have been pursuing.

We were involved from the beginning in the adefovir expanded access, since January, 1998, and we have had 64 patients registered; 56 started the drug; 20 are still on therapy today and a couple of them are actually here today and will speak to you. For all the patients treated with adefovir, the mean time on drug was approximately 9 months, which is the same as what the company reported. For the 20 patients who are still on drug at this time, their mean time on drug is 11 months. The shortest time on drug was 2 months for a patient who had to discontinue in order to take another nephrotoxic drug, cidofovir for CMV disease, and 2 patients were on for 3 months. One of whom was lost to follow-up and one of whom chose to go off all drugs.

In the rest of the cohort, the major reason we did stop was nephrotoxicity, the protocol designated cut-offs for those patients. A number of these patients had creatinine increases greater than 0.5 mg/dL from baseline.

Most of the patients had some proximal renal tubular dysfunction and needed replacement of phosphates and bicarbonate, and handled that very well. In every case where we stopped the drug the creatinine returned to baseline in anywhere from 2 weeks to 2 months. We had nobody who had continued renal dysfunction.

For the most part, I have used adefovir in a multi-drug salvage regimen, the so-called megaHART. There have been a number of cohorts that have been described extensively at meetings. We reported on our cohort at the salvage therapy meeting in Toronto last May, and all of these patients were on adefovir. There were 33 patients and they had a mean antiretroviral experience of 73 months, ranging from 36 to 120. They had taken a mean of 9 drugs, ranging from 5 to 11 drugs. All were failing their previous HART therapy. They had mean plasma viral loads of about 21,000 copies/ml and a mean CD4 of 153, which was an elevated CD4 for most of those people from where they had started antiretroviral therapy.

Patients were started on regimens of 2-3 NRTIs, 1 NNRTI, 2 PIs, hydroxyurea and adefovir. They had been treated with almost every drug class at that point except nucleotide analogs. There was 1 patient who developed pancytopenia within 2 weeks which we thought was due to hydroxyurea, and we didn't follow him after that.

Seventy percent of these patients achieved plasma viral loads less than 500 copies on 2 or more readings. Just to speed up, almost 40 percent of patients had undetectable plasma viral loads for 7 months or more at the time that I reported this trial. One patient was undetectable for 10 months at that time, and now has been undetectable for 18 months. Most of the patients actually tolerated these regimens really well despite what you have heard from some people, and some of that may have to do with the fact that these are highly motivated patients who were self-selected because they thought they could stick to a regimen like this and they were people who were desperate.

I think our results are better than some of the other cohorts because we have actually been following these people so closely. But in every instance when we stopped adefovir we had some increase in viral load, and that is what convinced me that this drug does have some efficacy because across the board every single patient had some rebound, not to baseline but it was a significant change from where they had been at the nadir.

Most of these patients thought adefovir was actually the most tolerable drug that they were taking. I think from the patient's perspective it is a very tolerable drug. I think where the challenge is, is for physicians because of the need for close follow-up but, like Charles, I

think that we do not really have a lot of problem convincing people that they needed to take electrolyte replacement. If they didn't want to take it, that they shouldn't be on the drug. If it was too complicated to come in monthly, they didn't take the drug. And, I think that is something that I have heard from other people. It is fairly easy to talk to patients about.

There have been a number of people who have voiced concern about the ability of doctors in the community to administer this drug properly. I think it is time we all realized that all the drugs we are giving are as toxic and as difficult as cancer chemotherapy -- and my brother, the oncologist, says "we like chemotherapy." And, we have a lot of responsibility when we are giving these drugs to know what we are doing. I think we can feel fairly protected by some of the things that the company has expressed that they are willing to do. I think that that will make a big difference as far as the educational campaign.

Finally, I think that conditional approval is appropriate here. I think that this drug has proven its efficacy in my patients. I think that it is well tolerated by them. It is certainly not a home run for treatment but we have more and more patients, as Charles mentioned, who have failed everything, who need the bridge to the next set of approvals. We won't have access to a lot of new drugs

until maybe the middle of 2000 or 2001. I think if we can get 8-10 months out of using effective regimens that have adefovir in them that that will help bridge that gap for a lot of patients. Thank you.

DR. HAMMER: Thanh you very much. The next speaker is Dr. David Hardy.

DR. HARDY: My name is David Hardy. I am from two places. I practice medicine at the Pacific Oaks Medical Group in Los Angeles, a large private practice specialized in the care of HIV-positive persons, and also has a clinical research component with it, and I also do research at UCLA School of Medicine.

I am here today to give my testimony in favor of the accelerated approval for adefovir dipivoxil for the treatment of HIV infection in nucleoside-experienced patients. My experience with adefovir stems from 1996 when I was a local PI for the GS408 study. We enrolled 52 patients at our site, had one of the largest enrollments in the study, and continued to follow the patients throughout the majority of the study duration through 1998, when all patients went off.

It was surprising to me that 408 actually showed something important, primarily because of the fact the study was being carried out during a time when antiretroviral therapy was in great flux, between 1996 and 998. Many of

the patients were in reality failing their therapy when they came into the study and had very, very poorly suppressed viral loads and were put on the trial as a sort of last-ditch effort. The therapy for many patients was really suffering from a learning curve. Many physicians were trying to learn how to use antiretroviral agents, and I was surprised there was any kind of cumulative effect at all seen in that trial because of its design flaw of adding one single agent to a failing regimen. But, in fact, it did show something important which I think we can all learn from now.

I also participated in the GS4150 study, the intensification trial. As an investigator with that study, trying to bring viral load down below 400 in those who were between 50 and 400, and also the private practice I work with has enrolled over 85 patients in the expanded access study among 13 physicians in our private practice group in West Hollywood, Los Angeles, and we still have over 43 of the 85 patients still on the drug, with a median follow-up of around 6-7 months. We have seen no severe or irreversible toxicities among any of those patients.

I think it is important today to focus on the patient population for whom this drug is being considered and the currently available options for this patient population specifically. I am not certain of this, but my

recollection is that this is the first time this advisory panel has ever considered an investigational antiretroviral agent to be specifically used in treatment experienced patients, those who have proven nucleoside resistance, at least AZT and 3TC and this is, hopefully, the beginning of a new era in the continued evolution of antiretroviral therapy and we are considering patients who have few options as opposed to those who have lots of options with being naive to antiretroviral therapy.

For those of you around the table who treat HIV-infected patients, I ask you to honestly think about the data upon which you make your decisions when constructing antiretroviral regimens for your patients who have genotypically or phenotypically proven AZT-3TC or 3TC resistant virus. How many agents do you know of that have proven efficacy with clinical data for this kind of genotypic analysis at baseline?

I believe the data we saw this morning starts to create some of these guidelines about how to treat patients with resistant virus. We haven't actually had any kind of data before to use in terms of creating therapies for these patients. The niche that adefovir dipivoxil is starting to fill is the previously avoided patient population, those who have resistant virus by genotypic proof or phenotypic proof due to prior drug failure. It is reassuring to me today to

see that both Gilead and the FDA demonstrated that the M184V mutation did, in fact, increase the sensitivity of AZT resistance virus with a significant decrease in viral load at 24 weeks.

Why and how adefovir causes this phenomenon with AZT resistant viruses is not entirely clear, but it does seem to work better here than it does in wild type virus. I think this is precisely where the new drugs are needed in the future, treating patients with resistant virus not those for whom we already have lots of available agents, such as wild type viruses.

On thing that I think seems very clear is that this medication does seem to be used with an agent concomitantly that causes and maintains an M184V mutation to optimize the efficacy of adefovir like 3TC, abacavir and perhaps FTC in the future.

As far as toxicity goes, one of the very first cases of clear-cut Fanconi syndrome occurred at our site in 1997 in a patient who fell in the cracks between week 24 and week 32. This patient was, in fact, hospitalized because of his Fanconi syndrome, had a creatinine peaking over 5 mg/dL, a phosphate that plunged to 0.7, and was in the hospital for over 2 weeks but did, in fact, survive.

Based upon this, and the occurrence of this same kind of problem in subsequent patients, it was, in fact, I

think important to note that physicians and the persons who help take care of their patients can, in fact, learn from incidences about toxicity to better follow their patients with appropriate follow-up care. I think an important point to say is that adefovir can be used safely in patient populations which need that kind of alternative therapy. Thanks.

DR. HAMMER: Thank you very much. The next speaker is Dr. Philip Kaiser.

DR. MARGOLIS: Well, I am not Philip Kaiser. I am David Margolis. I am an associate professor at Texas Southwestern. Like a previous speaker, I didn't really want to be here today either but, since I was the only one from our group that could attend and I thought there were some important points to be shared, I thought I would share that expanded access experience at the Parkland Hospital with you.

I won't go over points made by the previous speakers because many of the ones that I would make are similar. But the Parkland HIV Clinic is a typical urban clinic and follows more than 3500 patients of a wide variety of backgrounds. The success we have had with the adefovir expanded access program I think should be pointed out.

There have been 82 patients treated in the expanded access program, and 20 of them have left the

program, 4 because of reasons unrelated to adefovir at the patient's request. Interestingly, 7 left because they either had no response or disease progression or genotype testing became available that suggested other agents might be more useful for them. Then, there were 9 adverse events, of which only 5 were renal related: 1 proteinuria, 1 hematuria, and 3 rises in creatinine, 1 in the setting of lymphoma. There were no adverse events that were severe or irreversible.

That leaves 61 patients that remain on therapy and I don't have the detailed virological data but there are 62 patients that are at a very advanced stage of disease, on the average have used 8 antiretrovirals in the past, and those 62 patients have been on therapy for an average of 20 weeks, 8 of them for more than 36 weeks.

So, I think this just illustrates the point that in a very busy, demanding clinical situation, perhaps exactly the setting where you would think that management of this drug would be difficult and that provision of benefit using this drug would be difficult for patients, that is not necessarily the case. Thank you.

[Dr. Margolis noted off record that he had received Gilead travel support]

DR. HAMMER: Thank you. Dr. Joseph McGowan?

DR. MCGOWAN: Thank you. I would like to thank

the committee for giving me the opportunity to speak briefly about my clinical experience with adefovir. I have also received travel support to be here today.

My name is Dr. Joseph McGowan. I am an infectious diseases specialist at Bronx Lebanon Hospital Center in New York. I am assistant professor of medicine at Albert Einstein College of Medicine as well. I am the director of HIV ambulatory care for our hospital's AIDS program. Many patients infected with HIV in the community that I serve are highly antiretroviral experienced, and issues of drug resistance and salvage therapy have been paramount since the introduction of highly active combination therapy.

My use of adefovir dipivoxil has been exclusively as an agent available in expanded access. At my site, we have enrolled a total of 68 patients for expanded access for adefovir since January of 1998, and 67 individuals actually began treatment and 37 remain on treatment. Before the initiation of an adefovir-containing combination, the average number of prior regimens used had been 6.4, with an average of 4.4 prior nucleoside analog reverse transcriptase inhibitors and 3.3 prior protease inhibitors, and one-third had prior NNRTI use as well. Salvage combinations contain a mean of 5.3 drugs and only 13 percent were able to add a new nucleoside analog and 40 percent a new PI. However, due to inter-class cross-resistance full activity was not expected

from these agents, and we do not have access to either genotypic or phenotypic resistance testing in planning new therapies.

The average time on adefovir overall has been a mean of 164 days, ranging from 15 up to 603. For those who discontinued drug, it was 186 days, and for those continuing on drug 146 days. I have tried to always combine adefovir with 3TC when feasible in order to sustain the M184V mutation which may enhance the activity of adefovir, as we have seen. Most of the combinations used have included a non-nucleoside since our patients are relatively less exposed to this class of drug, and generally consisted of triple class salvage therapy with the addition of adefovir.

Initial responses to combinations that have included adefovir and efavirenz were impressive, with 87 percent of patients having a decrease in viral load of at least a log and 43 percent achieving a viral load under 400 copies by 13 weeks.

The reasons for permanent discontinuation of adefovir were progression of HIV disease in 9 individuals, loss to follow-up of 8, patient requested to discontinue combination therapy in 6, and concurrent use of foscarnet in 1. We had 2 patients who permanently discontinued for adverse events, a combination of proteinuria, hypophosphatemia, increased blood pressure in 1 patient, and

1 who had blurred vision and dizziness. I have seen proximal renal tubular dysfunction commonly and somewhat predictably, however, only one patient, as I mentioned, required permanent discontinuation as a result. No patient has had permanent renal failure, and most have returned to a baseline renal function by 2-4 months with either holding or dose reduction of adefovir.

I have been fairly aggressive in repleting phosphorus and potassium if needed. If I see a downward trend in phosphorus in from the monthly labs I will begin repletion early, even when phosphorus levels are above 2.5. I can't be sure, but I believe that this has prolonged usefulness of the drug. I will hold combination therapy with adefovir in patients who are responding if the phosphorus drops below 2, aggressively replete phosphorus, push all hydration, monitor urinalysis and chemistries during the period off drug, and often prompt attention will lessen the time off drug, a correction of 2-8 weeks in most cases, at which time combination therapy can be reinstituted with continued phosphorus supplementation, which I continue giving them even when they are back. I have successfully been able to regain viral suppression in this way in some patients. I have one patient in particular who initially had to discontinue drug after 6 months for proximal renal tubular dysfunction and increased creatinine and has had 10

months of viral suppression after restarting combination therapy including adefovir.

Overall, I feel having adefovir dipivoxil available will benefit patients living with HIV infection in need of options for salvage therapy. As mentioned, it will not be an agent for initial therapy due to its adverse events profile, however, I do envisage that with proper monitoring by experienced practitioners long-term therapy is possible with this agent in patients whose HIV drug options are severely limited.

DR. HAMMER: Thank you very much. Next speaker is Peter Hale.

MR. HALE: Thank you. My name is Peter Hale. I am from Los Angeles. I am editor of a new treatment publication, being launched next year by AIDS Healthcare Foundation. I am very pleased to be here today because I think this drug should be approved.

I realize that we have all seen a lot of data this afternoon. Some of it would seem to go in different directions and some of it sometimes would seem to be conflicting, and certainly there was a lot of background clutter with different antiretroviral regimens as backdrop with drugs being added and changed and different doses involved but, certainly, I am not an expert but if I were I would find it very difficult to make sense of all the data I

have seen today.

My own experience has been much more simple. I took adefovir as part of the expanded access program, and I thought that I did really well on the drug, even better than expected. I believe there are many other people in the same situation as myself who had a good experience on the drug. I had not failed virologically any combination regimen but I had failed protease inhibitors. Certainly my doctor felt that way. After two months of starting a protease inhibitor my glucose went through the ceiling and I ended up in the hospital. I became fully insulin dependent, and over a period of two years I had to increase that insulin from 30 units a day to over 120 units of insulin a day.

Earlier last year my lipids were out of control, and even with cholesterol lowering drugs my doctor started to worry about running into coronary heart problems. Hypertension developed just at the beginning of last summer so suddenly I was on medicine to lower my blood pressure.

So, the plan was to get off indinavir specifically, and the plan was to go to a non-PI-containing regimen, with sustiva efavirenz anchoring that new regimen. I am very highly AZT-3TC experienced, so I was coming off AZT, 3TC and crixivan and was very surprised that that regimen was holding up. I was undetectable. Anyhow, we stopped the crixivan and we started first with adefovir, and

we also planned to intensify with abacavir. So we did that. We started with adefovir and abacavir. Four weeks later, or six weeks later when we were worried about the hypersensitive reaction to abacavir -- we were looking for that -- we added sustiva. I could not start sustiva. We tried on three separate occasions two weeks apart to start sustiva, and the nightmares and CNS side effects were just simply -- they were extreme. So, I was stuck with three nuke and one nucleotide combination without a PI and without a non-nuke, and I stayed undetectable on that combination for six months.

We all know that adefovir is very easy for patients to take. I didn't feel anything. My lab values stayed over the normal ranges for the first five of those months. I had no elevation in creatinine. On the fifth month my phosphate dropped to 2.1 which, I understand, is not super low. We had the nutraphos right there so we supplemented with that straightaway. There was a trace of protein in my urea half way through the fifth month, if I remember. I was being monitored monthly, not just blood draws but also with urine analysis. There were no abnormalities, other than that trace of protein on the fifth month.

So, I have to believe that there is some antiretroviral efficacy if someone who is as experienced as

I am on AZT and 3TC can stay undetectable for six months on AZT, 3TC, abacavir and adefovir, without a non-nucleoside and without a protease. We switched off that regimen, if only because the data on aprenavir, as it was coming through, suggested that for me, with my background on protease inhibitors, it was worth a try. So, we made that switch. The reason I came off the drug had nothing to do with nephrotoxicity. We were very aware of kidney problems and at the first hint of any trouble we would have dropped the drug.

I forgot to mention that not only was I able to stay undetectable during that period, but my lipid levels returned to normal within six weeks of starting that combination and they have remained normal since. I take no cholesterol lowering drugs. I was able to stop my meds for high blood pressure within two months, and my blood pressure is normal also.

So, I think there is a niche. Whether it is for people failing a combination regimen in the conventional sense of virologic failure and breakthrough of viral load, or somebody like me who wants to simply get off and get onto some other combination to avoid the toxicities, which are very real and not imagined, caused by other agents.

I hope very much that this committee will approve this drug on the basis proposed, conditional approval with

good monthly monitoring of laboratory values. Because the toxicity is such an obvious one -- it stands out like a sore thumb -- I believe it is very easily managed, and with the education that Gilead is proposing the physicians and other healthcare providers will be aware of it. Thank you.

DR. HAMMER: Thank you very much. The next speaker is William Bahlman.

MR. BAHLMAN: I always like to do something a little different. I want to salute the doctors who took the time to come down here for this hearing today. I think it is very important to have doctors, who are on the front--line using the expanded access programs, here, at the FDA hearings. It is very important. I want to thank Peter Hale for his comments. I agree with all the comments that have been made so far very, very strongly. I have known Peter for some ten years and, thankfully, he is still around to be with us and advocate for this drug here, today.

I also received a sponsorship from Gilead to attend this meeting, against my lover's demand that I stay in New York to celebrate Halloween with him. It has been four years that we have been together and we haven't had one Halloween together, which is his favorite holiday. So, I am here under protest.

My name is Bill Bahlman. I am a founding member of Act Up New York, and I have served on the committee

advisory board of New York University Bellevue Hospital's AIDS program for several years, and I am an officer on that advisory board. I am also a 14-year survivor of AIDS.

Act Up New York, along with Project Inform and a couple of other organizations, helped craft the expanded access and accelerated approval programs that we have talked about so much here today. So, I feel a very close part of all of these discussions here, as we have worked so hard to put those programs in place.

I am not a doctor. Unlike some other community advocates, I do not play one at this podium nor anywhere else, for that matter, and I have continually fought for the right of doctors and people with AIDS to make their own choices about how to treat this disease.

I just got back from the European AIDS conference in Lisbon where, I am happy to say, according to the Euro-SIDA study most all of people with AIDS are currently being treated with three or four antiretroviral drugs as part of a HART regimen.

On the disturbing side, one prominent British researcher argued that antiretroviral therapy should not begin until a patient's CD4's fall below 180. Fortunately, this same researcher granted that when one starts therapy should be a matter of personal choice.

That is what I am arguing here for today --

patient choice and a doctor's right to use the drugs he or she feels are needed to maintain the health and life of their patients. It appears as if this is a controversial accelerated approval hearing. I hope I am preaching to the choir here that this drug should be granted accelerated approval. I hope that is the case. You know the data and I need not dwell on it, except to say that I believe there is clear activity of this drug against the virus, and that the modest but real impact of a new anti-HIV drug can be difficult to show beyond all doubt, particularly in patients who have been heavily pretreated, but that doesn't deny the drug's effect.

The question before you today is do we still need drugs with a modest but real impact against the virus. I firmly believe we do. You have before you a community consensus statement and two position papers, one from Project Inform and another one from Ron Baker's HIV and hepatitis web newsletter. He was formerly the editor of BETA, which was from the San Francisco AIDS foundation. So, he is a very prominent writer in our community.

I agree with these statements and their support of accelerated approval. In the debate among community advocates in the last couple of weeks, I heard one community advocate say, "I wouldn't give adefovir to my cat." I wouldn't give any of my AIDS drugs to my cat. I have heard

it said, "I wouldn't want to ever take adefovir." I don't want to take any of the four drugs that I am currently on but I do. I want to stay alive, and I am 100 percent adherent to my regimen. I haven't missed a single dose in the 23 months that I have been on HART regimens of two protease inhibitors and two nucleoside analogs. My viral load has been below 50 by both bDNA and PCR every monthly time period for the last 20 months. My CD4s are over 700 even though my baseline viral load was 143,000.

The entire HIV advocacy community pushed Gilead very hard to establish an expanded access program. About nine thousand people have gained access to adefovir through this program. This alone clearly shows a need for this particular drug. When I say we pushed Gilead very hard, I want to say that establishing expanded access programs does not happen by accident. It does not happen by regulation in terms of a company saying, "okay, we've reached Phase II, we're going into Phase III, now the program's going to begin for expanded access." It never happened that way in the past. It doesn't happen that way now. It is not going to happen that way in the future. It takes very, very hard work by a coalition of AIDS advocates to get the drug company to agree to do these programs and to get them up and running, and to see that they are maintained well. It does not happen easily. My concerns are if this drug doesn't get

approved today, what kind of message does that send to the industry about running a program that reaches as many as nine thousand people with AIDS?

Expanded access offers a unique opportunity to educate doctors on how to use and monitor for toxic effects of a new drug. Over 2000 physicians, representing over 70 percent of HIV prescriptions in this country, have participated in the expanded access program. I argue that these same doctors, already educated in the use and monitoring of adefovir, will probably represent over 90 percent of prescriptions postmarketing.

As a side note, amprenavir, which was approved by the FDA about six months ago, has to this date been used by significantly less people with AIDS than adefovir has. A recent study has shown worse adherence to amprenavir than indinavir.

My position is to strongly support accelerated approval. It clearly shows activity. Adefovir is a novel compound with a novel resistance profile. People with AIDS who have been heavily pretreated have shown that there is a profound need' for this drug. This advisory panel has done a very good job over the last years. You have supported the approval of abacavir and other drugs even with a minority of community opinion being opposed to approval. Every drug you have recommended approval for has remained a vital life and

health saving' option for people with AIDS. Not a single drug has had to go off the market; not a single drug has not shown that it is continually needed by people with AIDS to save alive.

The market, doctors and people with AIDS continue to make more intelligent decisions about treatment as well. You have done the right thing in the past. I urge you to continue with your legacy, you can justly be proud of. Thank you very much.

DR. HAMMER: Thank you very much. The next speaker is Max Delgato.

MR. DELGATO: Good afternoon, everyone. My name is Max Delgato. I live in Baltimore. I work for the federal government as a translator. I received support for transportation to get here.

I tested HIV positive in September 1989. I did not receive any treatment until July of 1998. At that time, my viral load was 120,000 to 127,000. After four weeks of treatment my viral load went down to 858 and after 12 weeks I am undetectable. I am still undetectable. My CD4 count was 346 when I started, or 21.7, and at the present my CD4 count is 571. Due to my treatment's compliance I experienced no side effects. I gained weight, 10 lb, believe it or not, and I look forward to this medication on the market. I will appreciate it. Thank you.

DR. HAMMER: Thank you very much. The next speaker is Timothy Christy.

MR. CHRISTY: Good afternoon, ladies and gentlemen. I have been on the regimen for about 11 months now -- over a hear and a half, and when I first started -- well, before that, about 10 years ago I was on AZT and it never bothered me -- just a little bit. Then I have been on some of the other drugs and some bothered me and some didn't, but the worse one was Viracept, and I had to get off that. Then my physician told me about the clinical program that was being offered by Gilead Sciences and I told him, sure, I would be willing to go on that program, and that was a year and a half ago. My viral load I think was about 24,000 and my CD count, whatever it is, the blood count, I think 192. And, I have been undetectable. Well, the first month after that my viral load went down to 400 and now it has been undetectable ever since, and my last checkup was 4 weeks ago, and my blood count was over 500, and before that it was 400-and some odd. My blood pressure has been normal for years, even before I found out that I was HIV positive, about ten years ago.

With the newer drugs, I have had no bad effects at all, only the first time when I took the sustiva, it made me very dizzy the following morning. It was like being hit by Dan Marino and Steve Young and Jesse Ventura all at one

time. But after that it was fine. So, I have no problems at all. In fact, I have very, very little reactions and I keep to a very strict regimen with that, every 12 hours, and I make sure I take that at a certain time, between 8:30 and 9:00 in the morning and 8:30 and 9:00 in the evening, right after eating I take these.

I want to thank Dr. Howard Grossman for his help. He has really been an angel of peace and a faithful guide to me since I have been with him. I want to give heart-felt thanks and my gratitude to the people at Gilead Sciences for coming up with this drug. I feel that you should approve it. I mean, I don't think many of us would be alive today if it weren't for these new drugs that have come about. As I said, I have had no repercussions from these drugs at all. I don't know any of these technical terms. I am not a medical doctor, I am not acquainted with all these. I just go every four to five weeks for my checkup. I listen to what the doctor has. You know, I am one of these people who go through the "white coat syndrome" when I go to my doctor and I follow whatever he says, and his advice and that is it. So, I hope very much that you approve this drug and all these new drugs to help people who are HIV infected. And, that is all I' think I have to say.

On a lighter note, I just want to congratulate the people in Washington for the victory of the Washington

Redskins, and my condolence to the supporters of the Oakland Raiders on their loss to a superior team.

[Laughter]

DR. HAMMER: Thank you very much. Our next speaker is Hosam Chreim.

MR. CHREIM: My name is Hosam Chreim. I am from New York City. I received travel support today to get here. I am 34 years old. I contracted HIV 13 years ago. Since then, I have been on almost every drug to fight this disease. The virus was building resistance to the drugs that I was taking, and adefovir was a different type of drug. My doctor put me on adefovir along with two other antiretrovirals and a protease inhibitor a year and a half ago. Since then, on the new combination my T-cells have been rising from below 200 to above 400, and my viral load, that once was over a million copies, now is between 2000-4000 copies.

I have had very little side effects, but overall I feel very good. Every time I feel that I am at the end of the rope, a new drug comes and prolongs my life. To many of us who have been fighting this disease for a long time, this may be an additional treatment until a cure for AIDS is found. Thank you.

DR. HAMMER: Thank you very much. Amy Sullivan?

MS. SULLIVAN: Good afternoon. I have received

travel support to be here today, but no financial interest in the company, and out of respect for the panel I will try not to picture you in your underwear since I am a little bit nervous.

[Laughter]

DR. HAMMER: That is a unique comment for this committee hearing but it does create humility on our side. Thank you.

MS. SULLIVAN: I am the director of clinical research for Pacific Reiser Medical Group in San Francisco. We are a group of healthcare providers who treat over 800 HIV-positive men and women in the Bay area. We are also very active in clinical research for ART drugs to treat HIV, and currently participate in a dozen or so such trials.

We had the opportunity to be an investigative site for adefovir dipivoxil expanded access program. I was the coordinator and primary patient contact at our site since the program's inception in early 1998.

I would like to share with you some insight I have gained about this drug and its impact on our patients. We had a total of 27 patients on study. Those of you in industry know that when a drug is put on expanded access it is the sickest people that enroll first, the patients who have burned through almost every other drug available.

I spend a lot of time with each patient when

putting them on a new regimen. It is vital to patient compliance and comfort to thoroughly explain both how to take the drug, including dosing and nutritional requirements, and also what to expect. This became especially important with adefovir. There has been no lack of discussion today of this drug's unique toxicity profile, but from a treater's standpoint, the effort to educate patients about adefovir treatment should really be no different than any other new antiretroviral therapy that the patient is prescribed.

We explain to patients up front the possibility that they may begin to experience lab toxicities around the fifth month of treatment, and that they will be monitored closely for these changes. Because we are working with patients that don't have many more treatment options, this risk has never been a deference to them.

The adverse effects of adefovir are not a mystery. They are predictable and easily monitored. As we gained more experience with this drug, we became more comfortable with monitoring and managing toxicity. In the course of the adefovir expanded access program, two things about this drug have impressed me and the patients that we treat.

First, the simplicity of dosing -- one pill once a day, no nutritional requirements. Patients are generally incredulous when I review dosing with this drug.

Secondly, the absence of side effects. The few patients we eventually took off study for toxicity reasons were virtually clinically asymptomatic. The rest of the group had very few, if any, side effects attributable to adefovir.

These two aspects of the drug have a profound positive impact on quality of life for people living with HIV, which is one of the main goals of HIV therapy in my eyes. Let me. remind those of you that don't lay hands on patients on a daily basis that people are still dying from AIDS. Let's not lose sight of the fact that we have the opportunity to make this drug available to many more people battling HIV., If we can extend their lives and increase their quality of life by any degree, I feel we have a responsibility to do so and, therefore, support this NDA. Thank you.

DR. HAMMER: Thank you very much. Juaquin Sanchez? Is Juaquin Sanchez here?

PARTICIPANT: Juaquin wasn't able to make it. He is in Los Angeles.

DR. HAMMER: Thank you. The next speaker is Francois Ouliez.

MR. OULIEZ: Mr. Chairman, my name is Francois Ouliez. I am one of the directors of the European AIDS Treatment Group, and co-chair of the European community

advisory board. Today we don't call it Halloween in Europe but All Saints Day, where we celebrate the memory of all those who died in the past. So, the question I am wondering about today is whether or not this product could have made a difference for the people who have recently died of AIDS, or those who are expecting new options to avoid death in the following months.

I received travel support from Gilead Sciences. I was wondering about the lack of real CD4 response in the trials that we saw this morning. Since, in a heavily treated population the CD4 response is a strong predictor of progression to AIDS, when we discussed this point with my colleagues last week in Lisbon, we were really wondering if this drug could be of any benefit to patients with AIDS.

Soon we will have to express our opinion to the European Medicinal Evaluation Agency on this new compound. Allow me to summarize what this opinion could be if this review by the EMEA would take place in November, 1999.

First, one crucial question, what do people need today for their treatments? More potent treatments; more potent regimens, with a longer duration of viral replication control, and treatments that respect the quality of life; treatments that are efficient in heavily pretreated patients; and treatments that have limited toxicity, or at least that don't add any toxicity to the available products.

The question is, has adefovir one of these added values compared to available options? If yes, if only one out of five of these values is met, then approval should be considered.

First potency, potency in experienced patients. There are some trends, some indications that adefovir could be very active in these trends harboring the M184V mutations. This was assessed in a substudy, and so far a trial design to evaluate this benefit in terms of viral load has not been conducted properly. This potent synergy between adefovir and the M184V mutation has not been properly evaluated. As I say, the CD4 response has not been very impressive. Nevertheless, the need for immune restoration is crucial in NRTI pretreated patients.

Second, duration -- one pill a day for modest activity. Maybe this is the minus 0.3 log that could make the difference in order to maintain HIV RNA below 50 copies for a long time. Has this been shown in clinical studies? Not yet. Long-term studies like the other trial in Europe could not conclude, mainly because of the new context in HART. But the sustained antiretroviral activity is balanced by the discontinuation rate, 40-50 percent at week 48.

Quality of life -- one pill a day, whenever you want, with no food effect. That seemed okay. Many people can support that. People are so afraid to stop all

treatments even if all treatments failed, and one pill a day is still something most reluctant patients regarding treatment can stand. But quality of life is also a matter of tolerance and safety. What about monthly monitoring when you are on holidays? What about monthly monitoring in summertime when all settings are closed in Europe, for instance?

Toxicity, grade 3 or 4 serous adverse events were, at minimum, 5 percent across all trials. New products, new PIs, even maybe EPMPA may suffer from renal toxicity with adefovir. We don't want to jeopardize the use of future PIs which will be limited through renal filtration. After the blood, after the bone marrow, after the liver, after the pancreas, after the CNS, after the endocrine system, after the cardiovascular system, and now the kidneys. We would prefer to keep our future options open.

Many questions were raised. What about monthly monitoring? What about long-term toxicity? What about mitochondrial toxicity related to adefovir? Is the carnitine supplementation accurate? Does it really correct the depletion? What is the impact of this depletion? We don't have a clear idea.

For these reasons, we would recommend approval for adefovir if the activity in 3TC or abacavir pretreated patients will have been demonstrated in a prospective manner

with a true viral load benefit. If 60 mg daily would definitely prevent the risk of high grade renal toxicity. And, what about 30 mg? What about 10 mg? If a longer-term toxicity profile could exclude any other toxicity. Adefovir mitochondrial toxicity should be better evaluated. If we could have the certitude that doctors would be properly informed about the guidelines to monitor the toxicity and respect them.

Because of the late submission of the application to the EMEA, we may revise our opinion when Phase III trial results will become available and when the EMEA will evaluate this product later next year. But, as of today, November 1, 1999, we would not recommend approval. Thank you.

DR. HAMMER: Thank you. The next speaker is Michael Marco.

MR. MARCO: Hello, there. I figure that I can take the podium since I am the only person here who has received no financial support. I at least deserve this since I had to use my travel budget, which is very small, in Treatment Action Group.

Treatment Action Group has a position paper that we have out on the table, and I know that the committee members have seen it. I promise the committee members that I will not read the whole thing for you because it is eight

pages, but it has great references at the back. What I will ask you to do is just look at the TAG position on page one, and then on page five there is an excellent discussion.

Now, basically after you read it, I would also like you to look at the summary slides that Dr. Struble had in her presentation. The FDA's analysis was excellent and I feel that my tax dollars were hard at work, and I appreciate that. I also want to let Dr. Struble know that TAG has a job opening --

[Laughter]

-- if you would want to move to New York, we would have you. It is much safer now and we are a fun group of guys.

In the TAG position, it is unfortunate but as current data has shown, especially for the dose of 60 mg, we cannot support the approval. We do not believe it is effective nor safe for what it has been indicated.

There are just five major points to consider. The five major points to consider are truly in the questions that Dr. Hammer will be asking you shortly. Although 120 mg is not proposed for marketing, did the original adefovir development establish efficacy of 120 mg QD dose for the treatment of experienced patients? I think the answer is no. As we saw in the FDA's analysis, study 408 did not show a difference statistically from placebo. It did not show a

difference in the CPCRA study, nor in the ACTG study. I am one that believes that federally funded studies usually yield fairer results than industry-sponsored studies.

If you look at the subset analysis, that does look encouraging and we do want to see some further information about adefovir's activity in people with 3TC resistance. But you must understand this was a subset analysis, and to quote the FDA slide, exploratory subset analyses are only useful for generating a hypothesis, not for approval.

The two 60 mg studies plus the expanded access group are riddled with dropouts. The dropout rate, the discontinuation rate is huge. If you note, in the 60 mg dose only 73 patients -- I repeat, 73 patients have had more than 48 weeks of drug. That is not enough. I cannot go back to my community and tell people that this is safe when we only know that 73 patients have had this drug for 48 weeks.

I also appreciated Dr. Wong's concern during the question period when he was trying to tease out the 60 mg versus 120 mg in study 417 that was looking at it in combination with other antiretrovirals. As he said, was it no effect versus no effect? These are issues that you will want to weigh.

I must say that I am very excited about adefovir for hepatitis B, and I am actually on the ACTG protocol team

looking at this drug at lower doses, at 10 mg and at 30 mg. I hope that I can be back here in, say, 18 months to ask you to approve the drug if it does show activity and safety for hepatitis B. But today Treatment Action Group says that at this dose it is not effective nor safe for approval. Thank you.

DR. HAMMER: Thank you very much. The next speaker is Jules Levin. Jules yields. That is the end of the list of signed up speakers in advance. Is there anyone here who would like to make a statement as part of the open public hearing? If so, please come forward. If not, the open public hearing is closed.

What I would like to do is take a ten-minute stretch break. I would ask people not to leave the room unless it is mandatory. We are going to restart in ten minutes on the dot.

[Brief recess]

Questions to the Committee and Discussion

DR. HAMMER: I would like to call the committee back into session. This is now the point at which we consider the questions to the advisory committee.

A couple of points in advance, I am going to, as we should, allow each member of the committee to comment on each question. Because of the number of questions and the length of discussion that we have had antecedently, I would

ask that comments be targeted.

The fourth question on the list is the voting question today. The questions are designed for the audience and the committee to really reflect and parallel the developmental strategy of this agent which, as we have heard several times today, is a bit unique because it started at the 120 mg dose and then changed in midstream because of the nephrotoxicity. So, the efficacy and toxicity at 120 mg and the bridging strategy to 60 mg is reflected in the nature of the questions and in their sequence.

I would also mention that Drs. El-Sadr and Feinberg need to leave early. So, I am going to ask them to comment on question number one first, and also to make comments, if they wish, on the other three questions. But for the other committee members, I would say let's reserve discussion for each question in turn.

With that introduction, I will read the first question for the record. Although the 120 mg dose is not proposed for marketing, did the original adefovir development establish efficacy of the 120 mg QD dose for treatment experienced patients?

If yes, then with respect to efficacy, has the applicant demonstrated sufficient comparability between the proposed marketing dose of adefovir 60 mg and the 120 mg dose such that one can conclude that the 60 mg dose is

superior to placebo?

If no, what additional data are necessary to characterize the efficacy of the 60 mg dose of adefovir?

I will not read the other three questions at this time but, again, if Drs. Feinberg and El-Sadr wish to comment on them before they have to leave, they are invited to do so. So, let me turn to Dr. Feinberg.

DR. FEINBERG: All right, well, I will bite this bullet right away. I think the answer to question number one is no. I think that Gilead's 408 study, although it had a statistically significant difference, that difference strikes me as being, at best, sort of marginally clinically significant. Two federally funded studies were negative. Study 417 I think is beset by design problems that were well elucidated by the FDA folks, not to mention that close to a third of the data for the 120 mg dose in 417 were missing. So, that is my response to question number one.

So, I am obligated then to speak to question 1B about what additional data are needed to characterize the efficacy of 60 mg. I would start by saying that not only does the 60 mg but probably the 30 mg dose needs to be studied carefully in order to generate these data. Since there is already a recommendation in the proposed label that people would be dose reduced to 30 mg, rather than get caught up in this problem once again of not knowing what the

drug does at lower doses, it really should be tackled head on.

And, I think the only way this can be done is in appropriately controlled and double-blind fashion. I think there are a number of different ways to go about it. For example, other companies have recently shown that it is feasible and ethical to do a lead-in of a couple of weeks, two to four weeks of monotherapy dosing, especially with agents where there is reasonable data in hand that resistance doesn't develop rapidly, in a placebo-controlled fashion to sort of really see what does this drug at different doses -- I would say at 30 mg and 60 mg -- do on their own. It is incontrovertible to me that you need to know what bang you are getting for this buck, especially since this buck is going to buy you potentially a lot of nephrotoxicity.

I know a lot of people spoke from personal experience, both the physicians and patients, but I too have given this drug to a lot of people, both in controlled clinical trials as well as in expanded access, and my experience is not quite as cheerful, and I was almost starting to believe that the six patients with clinically significant problems -- that maybe half of them were mine. You know, it is not an inconsiderable kind of toxicity, and it is not an inconsiderable thing for people to be taking

replacement phosphate and magnesium for months after months after months. I have not seen ready reversibility so I am certainly concerned that we know that these drugs work if we are going to be offering them to patients with the potential that there is very real possibility of harm.

So, given that that is my answer to question 1 and 1B, I would just make some other comments for the other pieces of it. I do not think the safety profile is adequately characterized. It was frightening to me to see that the number of patients on the 60 mg dose of adefovir for 48 weeks totaled 73 people, 30 in a randomized trial and 43 out of the first 1000 in expanded access. I was very anxious about how thin that data set was. I do not think that the data indicate that reversibility has been definitively demonstrated for any dose of adefovir. I think it would be really critical to try to understand who belongs to that subset of patients for whom the toxicity is not going to be reversible. It would be wonderful if there were some way to identify the people at highest risk up front and avoid giving them the drug. It may be that time to onset becomes somewhat more prolonged with lower doses, but it does not necessarily follow that there is some absolutely clean dose. I don't know that we know that there is a clean dose of this drug.

That leads into this monthly monitoring issue. I

think that it is clear from the FDA presentation that there is a subset of patients for whom monthly monitoring of electrolytes is going to be inadequate. So, my concern would be to want to, again, have some data to make a reasonable guess on the part of clinicians to know which patients are going to need closer monitoring than monthly because I think there are definitely some patients like that. In fact, as we learned more and more about this and started intervening in patients as soon as their phosphate levels started dropping, you could not always necessarily ameliorate the problem by repleting phosphate and taking people off the drug, or lowering their dose right away. Some people seemed to slide into a more prolonged period of difficulty regardless of your moving quickly. So, I think it is important to do that.

My concerns about the proposed monitoring scheme, the management scheme, is that in the real world of treatment feasibility of providing drug on a monthly basis dependent on patients showing up for lab -- I don't think that is going to play well in all situations. There are a lot of patients for whom compliance is an issue. Maybe that means up front those are the patients who shouldn't be given this drug.

Then, that goes to question four, is 60 mg safe and effective,? Do the provided data establish this? I

think the answer to that is no. I think, therefore, my answer to 4A, what other data should be provided before reconsideration of this application, as I stated really in my answer to 1B, I think we need to know that 30 mg and 60 mg work. We need to know that unequivocally. I think, in addition to knowing that unequivocally, it is going to be critical to study a large enough number of patients. The actual numbers of patients in the controlled trials is really very small. So, when the presentation said over 5000 patients treated, we are really talking primarily about the expanded access. The total number of people in the controlled trials was, I believe from a sort of seat of the pants feel for it, less than 1000 patients. So, I think we need to see this drug studied in a large enough number of patients for an extended period.

In my mind, as I said last summer when we had the closed session, 48 weeks is the minimum duration of observation that you would want for this drug, especially if it turns out that the onset of nephrotoxicity is even a little more slow with 30 mg than with 60 mg. You just have to know that. That kind of decision-making up front on the part of patients and physicians is crucial.

I also think that it would be critical that future study populations be more diverse both by gender and race. This was primarily men and primarily not minority

populations. As I mentioned before, I am concerned about nephrotoxicity in particular subsets, although I know that the analysis the company did runs opposite to my feeling about that.

Then, what additional recommendations? I actually think it would be very important to study this drug in hepatitis B, HIV co-infected patients. That may be clearly a niche population for this drug.

I think other little bits and pieces will evolve with the rest of the conversation. I think that formally assessing viral load rebound in patients who have to discontinue the drug for toxicity in some standardized manner would be valuable. In other words, people who stop the drug for toxicity get a viral load at 1 week, 2 weeks and X weeks after that, and you get a series of standardized time points that you could look over a large population. That is kind of a backwards way of assessing the contribution of this drug to multiple drug regimens. I will yield there to Wafaa.

DR. HAMMER: Dr. El-Sadr?

DR. EL-SADR: This is difficult. I will start with the first question. I think the sponsor essentially is asking for proposed marketing for this drug for treatment experienced patients, and I think the three relevant studies for treatment experienced patients with the 120 mg dose are

the Gilead 408, the CPCRA 039 and the ACTG 359.

Based on using the preferred HIV RNA viral endpoint the FDA has recommended, the less than 400 HIV RNA suppression, there doesn't appear to be a benefit of adefovir at 120 mg in any of these studies, the three studies, and certainly there was no evidence of benefit on CD4 cell counts, which I think is a very valuable surrogate marker. Even if we take the sponsor's analysis of the 408 data, it is the only one that showed a positive effect with the 120 mg dose in treatment experienced patients.

So, I guess I am saying to number one that I do not think that the data support that 120 mg has established efficacy for the treatment experienced patients.

I do think though, in relation to 1B, that there is really a dire need for more data on the 60 mg dose of adefovir. I think there is a lot of interest in getting the data, and I think it is very important to get the data on the 60 mg dose, and I think the way to get the data is to compare 60 mg to placebo. The two studies that are being proposed by Gilead I think are the right studies to do. It will be very interesting to look at those results, both in terms of using the 60 mg in an intensification type of study, as well as also in "salvage" type of design in 458. So, 415 and 458.

I don't think the duration of follow-up in 417, as

we discussed today earlier, demonstrates either the efficacy or the safety of 60 mg of adefovir. I think it is too short to demonstrate safety and it is too short to demonstrate efficacy. I think the follow-up is too short.

To move on, I think I sort of answered number two. I feel like a minimum follow-up of 48 weeks is needed at least for the 60 mg dose. I think we always sort of look at the data from expanded access, but we all know the limitations of expanded access data. People who stop taking the drug in expanded access programs are really lost to follow-up most of the time because they remain in follow-up mainly because they are getting the drug. Once they are not getting the drug, often the company and the sponsor don't have data on those patients. So, I think it is going to be very difficult to get safety data or efficacy data from expanded access because there is always going to be a selection bias. You are following the people who have done well in expanded access, and I think, unfortunately, that is the nature of expanded access.

Therefore, I think the way to get at the data with 60 mg is going to be through clinical trials rather than expanded access, and it is going to be through studies like 415 and 456 and others so that we can really learn about the efficacy and the safety of this dose.

As for the renal management, toxicity management,

I really don't know whether there is any other option, other than monthly follow-up. I guess, by monthly electrolyte monitoring we are at least trying to identify early those who are developing some abnormality before it becomes very severe. It would be very helpful to try to identify risk factors for developing this syndrome. I know other people have tried, but maybe as we accumulate larger numbers of patients we can actually come up with a profile of the patient who is either at high risk or at low risk so we know, when we start a patient on whatever dose we are going to start them on, what the likelihood is of nephrotoxicity and, therefore, we can tailor the intensity of the follow-up.

I think it would be very interesting to pursue a little further the racial difference that was identified. I think it is fascinating, and probably the nephrologist can comment on that later on. I don't know why African Americans would be at less risk but I think it is very interesting and probably needs further pursuit.

I also think the management -- the whole idea of dose reduction is interesting although, on the other hand, we don't know that the lower dose is of any value. We don't know whether it is better to stop. Could we possibly be generating resistant virus by using suboptimal doses like 30 mg? I don't know the answer to that, but I think that can

be easily studied within the context of these trials, once a decision has been made to reduce or stop the current dose, to either stop the dose or to dose reduce, so that we can find essentially which is the better strategy.

In relation to question number four, again, I think the paucity of data on the safety and efficacy of 60 mg is quite obvious to all of us here today, and we need longer-term data. It is funny to think of longer term being 48 weeks but I think that is the minimum of longer-term data.

I think also there has been a lot of confusion today about sort of where the niche for the drug is. A lot of the patients who have been studied with adefovir have been not truly "salvage" patients. At least based on the context of the clinical trials, they have been primarily PI naive and antiretroviral naive, or some PI experience and mainly NNRTI naive, while most of the use, I am hearing, in the expanded access program has been in very experienced patients. So, there is sort of very broad populations that are being exposed to the medication, and I think the two studies that have been designed are probably going to be answering different questions for each of the populations that are very relevant -- the patients who are going to be sort of in an intensification mode and the patients who are going to be more treatment experienced and more of a

"salvage" mode.

I think there is a need to look at this drug and do drug-drug interactions. There are a lot of drugs used in HIV care that I don't think have been looked at -- I don't know if methadone has been looked at, or oral contraceptives, or trimethoprim sulfur, or NNRTIs, or all the other drugs in terms of the new proposed dose, the 60 mg dose, and that should really be done as we learning more about the dose.

I guess in the end, this is a very, very tough decision but I can't truly, in my heart, be convinced that there are enough data to support the safety or the efficacy of 60 mg. It is unfortunate because I think somehow this NDA was maybe prematurely submitted. The data is going to come and the sponsor is conducting and planning the right studies but I don't think we are there yet. Thank you.

DR. HAMMER: Thank you very much. I would like to turn to the other committee members. In turn, I would also like the committee members to just focus on question number one, the 120 mg dose efficacy issues. I will start on my right with Mr. Schouten.

MR. SCHOUTEN: With regard to the efficacy of the 120 mg dose, I can't ignore the CPCRA nor the ACTG trial either, and I think that given our standard criteria for efficacy being percent less than 400 or less than 50, I just

don't see the data given with the composite of all the studies at 120 to say that I can convincingly say that there is efficacy, given our standard criteria for efficacy. But, clearly, this drug does have some antiretroviral activity. So, I am torn. And, clearly, this drug is suppressing HIV to some degree but it is not meeting our standard efficacy criteria.

Regarding whether or not there has been efficacy of the 60 mg and 120 mg dose, I just think the design of 408 and 417 and the patient population is so different I just don't see how I can look at those two studies and saying that it has shown efficacy. I would like to see a very different trial design than 417. I would like to see a placebo arm, and that be the main variable comparing the 60 mg to the 120 mg, and have placebo or have more consistency in the patient population than there was on the 120 in the 408 trial.

DR. HAMMER: Thank you. Dr. Kimmel?

DR. KIMMEL: The question of efficacy is I think outside my area of expertise so I would prefer to pass.

DR. HAMMER: Thank you. Dr. Kopp?

DR. KOPP: I actually feel the same way. I will also pass.

DR. HAMMER: Thank you. Dr. Verter?

DR. VERTER: I probably should pass because it is

somewhat outside, but I will speak to it from a statistical perspective because I have a thing about 1B. Repeating somewhat what I said before, there were multiple ways of analyzing the data. I agree with -- she just left, but she said there were three studies in total and the data, just the data from those studies don't seem to suggest statistical efficacy. There does seem to be some viral activity but not statistical efficacy.

I am also somewhat troubled by the lack of one consistent measure of efficacy -- differences between medians, mean change between two time points, DAVG analyses and I think RNA and CD4. So, I urge Gilead, the FDA and whoever else presents data to this committee, whether I am on it or not in the future, to try to come up with some consistent measure, something that the community can accept, that the industry can accept and the FDA can accept. It will make everyone's job a lot easier.

With respect to 1B, I agree with the comment that I think the ideal stud -- semi-ideal -- would be a placebo-controlled 60 mg dose, but within that context I urge, if they are going to do it, or any other studies that are done, that as much as possible you get complete data on everybody.

DR. HAMMER: Thank you. Dr. Wong?

DR. WONG: I am going to disagree partially with those who have spoken before. I am convinced that the data

show that the 120 mg dose was effective, was efficacious. I understand that there were some conflicting results between the different studies but the 408 study convinced me.

I should comment that holding any investigator to a fixed criterion, such as the proportion of patients who achieve 400 or fewer copies of HIV RNA per milliliter of blood is probably -- I mean, it is certainly a reasonable criterion but it shouldn't be considered to be the only criterion. The HIV concentrations and the DAVG24 results that Gilead showed were convincing to me.

On the other hand, I think that the comparability of the 60 mg dose was not shown for the reasons that we discussed earlier. The design of the study was really such that it probably could not have been shown because of the multiple confounding factors, the small samples, etc. That is my answer to question one.

DR. HAMMER: Thank you. Dr. Pomerantz?

DR. POMERANTZ: Yes, I don't think that, unfortunately, I was convinced that 120 mg dose is efficacious for marketing, even though it wasn't put forward for that at this time.

There were a number of things, in deference to Dr. Wong, that I did take quite seriously, and I thought that the FDA's presentation actually took me from a borderline case to over the edge because I do think that getting below

400 copies is a very reasonable thing to look at nowadays. I think that there are drugs where it becomes somewhat more complex. The PIs have been shown in certain cases to have a clear effect on morbidity and mortality, not directly correlated in all patients to decreases in RNA levels, and that is an interesting concept, whether there is a change in the fitness of the virus and, therefore, that is different, but there is no data for that here. And, with that not there, I still would hold until someone shows that this drug has something comparable with the de-synchrony that has been shown in certain PIs that the 400 level be something that should be a reasonable earmark at least for the 120.

I also was really taken back by the amount of the missing data, and Dr. Feinberg has flown the coop, but I agree with her. I thought that 22-32 percent was surprising in relatively small studies, and I don't know where those people went but that is problematic when you have so few studies.

Again, this is a drug that has some strength to it, but a 0.3 log change has to have more than it showed for effects and still have problems with the data sets for me to go forward and say yes.

So, that being no, I agree that some type of placebo-controlled trial, certainly with other drugs, at 60 mg and, as Dr. Feinberg said, at 30 mg would be quite

reasonable to get at what they are asking for.

Just to go to number two, Scott, because it is related to it, I don't see that 60 mg has been shown either. There were very few patients over 40 weeks. There just wasn't enough to convince me that with the adverse effects that we have data here.

I want to make one last comment, and that is there is no doubt that the word "niche" is a good word for this drug in certain cases, and the sort of parade of very important anecdotal remarks that were made is interesting. There may be holes in the armamentarium where this will fit in for a particular patient, but dissecting that out in trials is sometimes hard, and I think the company has to decide what they want from this drug. Do they want an up-front drug that is used by many patients who are naive? Do they want it to be for people in their first salvage? Or, do they want to try to find a niche where certain patients will get help with a drug when all else has failed? I think they have to decide where they position this.

DR. HAMMER: Thank you. Dr. Jolson?

DR. JOLSON: I am sorry to interrupt. I just think it might be worth clarifying something about the endpoint issue so that there isn't a misunderstanding in terms of percent undetectable versus DAVG. Hopefully, they are all measuring the same thing, which is viral

suppression, but I don't want people to leave the meeting thinking there is only one way that the agency is willing to look at viral suppression.

In fairness to the sponsor, this study was designed several years ago, started several years ago, really before there was consensus on the goal of therapy, which is reducing virus to below -- what it is 400 or 50, what our current standards would be now. That is what our current guidance reflects. But I think this study was probably designed in 1996, something about that.

Also, even if it were started today, by design the study would really be unlikely to show, because of the way it was added as a single drug, percent undetectable. So, hopefully, when you are all considering this, you will just sort of factor that in terms of the time element and the study design. Hopefully, you will see that it is not that it doesn't meet FDA's current endpoint. We would ask you all to evaluate it as evidence in and of itself of viral suppression.

DR. HAMMER: It might also be worth commenting that the intrinsic potency of the agent and also the population in which it is being targeted make it difficult to use proportion below 50 copies as really the clear-cut endpoint. One has to use a mix of virologic endpoints here and change in RNA or DAVG have to be co-equally looked at,

just as an aside here, but thank you for the clarification. Dr. Lipsky?

DR. LIPSKY: In answer to question one on the 120 mg dose, I would say that there is suggestive evidence for some degree of viral suppression. I should respond a bit to the comment, "well, what about the 60 mg dose?" I think there is much less suggestive evidence on that.

What I would do is, if feasible, go back to basics here and wonder where did the 60 mg dose come from, except that it was half of 120 mg, and we are hearing about 30 mg and possibly lower -- if one could go back, if it is feasible, to their 402 type study and look at basic dose-response relationships and see how low you can get, I think they were using p24 in that study. One can be a bit more sophisticated these days, but to see how low one can get because, gee, what if 10 works the same way as the other, it would be unfortunate to have to, thus, go with a higher dose.

It seems like in a situation where there is a therapeutic index question, one would want to know very clearly the dose-response relationship of toxicity and the dose-response relationship of efficacy so as to maximize the therapeutic index.

DR. HAMMER: Thank you. Dr. Masur?

DR. MASUR: I think there is a lot to recommend