the saquinavir and RTI group, in which 60 mg was superior to the 120 mg. The results of group 3 had a disproportionate affect on the results of the pooled analysis, therefore, giving the appearance that the overall response rate is similar between doses.

[Slide]

Regarding safety, overall there is insufficient information on long-term administration of adefovir 60 mg. From the results in study 417, it appears that the time to onset for creatinine and phosphate abnormalities are delayed for the 60 mg compared to the 120 mg. However, there were no statistically significant differences for the frequency or resolution of nephrotoxicity between these doses in study 417. It is unknown if the incidence and time to resolution will favor the 60 mg dose with longer follow-up and sufficient number of patients.

Also shown in the expanded access program the onset of creatinine and phosphate abnormalities appear delayed. Approximately 40 percent of patients on the 60 mg arm compared to 50 percent of patients on the 120 mg arm will develop creatinine and phosphate abnormalities. There is a question if this difference is clinically meaningful to conclude that adefovir 60 mg is less nephrotoxic than the 120 mg dose.

In addition, the resolution of nephrotoxicity from

the 60 mg dose has not been fully characterized because there have been few patients and short duration of follow-up in both the 417 and expanded access program to assess this.

[Slide]

In our review of the submitted data, there appear to be several unresolved issues with respect to the proposed adefovir 60 mg dose. First, there is insufficient information available regarding the long-term safety of adefovir 60 mg since relatively few patients have received the 60 mg dose for more than 24 weeks.

Second, there are limitations in the design of study 417 that cast doubt on a definitive conclusion that the 60 mg is an active dose.

Finally, it is difficult to determine at this point which patient population will be appropriate to receive adefovir treatment, given the risks of nephrotoxicity and the limitations of the efficacy data available for the 60 mg dose.

Gilead has proposed ongoing approval trials may provide sufficient information to adequately address these unresolved issues. We look forward to your discussions today for these issues, and recommendations on the questions that are posed before you.

[Slide]

Before I end, I would like to acknowledge and

thank the entire adefovir-review team. Thank you.

DR. HAMMER: Thank you very much. We are going to enter the committee discussion period now. Questions for both the sponsor and the agency can be addressed during this period. As I mentioned earlier, I think there will be a fair number of questions. I would ask the committee members, in deference to their colleagues, on the first round here to prioritize your questions and ask only the two or three most pressing questions so we can get around the table. After that, we will open it up further. I will begin on my left with Dr. Bertino.

Committee Discussion

DR. BERTINO: Could the sponsor present their pharmacokinetic drug interaction studies with delavirdine and saquinavir, please, if they have that data?

DR. HAMMER: Please identify yourself for the transcriptionist.

DR. CUNDY: I am Ken Cundy with Gilead Sciences. Can I have slide 436, please?

[Slide]

I wanted to start off by just discussing a little bit more about study ACTG 359 in which an interaction was reported between adefovir dipivoxil and delavirdine and saquinavir. As you can see from the design of this study, all patients received saquinavir and either ritonavir or

nelfinavir. In addition, they received delavirdine, adefovir or a combination of the two drugs. The pharmacokinetics was evaluated in the 6 different cohorts in 7 patients per arm.

[Slide]

This slide illustrates how complex ACTG 359 was in terms of the background drug interactions between delavirdine and the protease inhibitors that were used. As you can see, delavirdine has direct effects on the pharmacokinetics of saquinavir and ritonavir, and it also has effects on nelfinavir. However, you can see that saquinavir itself has reverse effects on nelfinavir, and nelfinavir in turn has reverse effects on delavirdine. So, in terms of this being the background in which adefovir was introduced, it makes things fairly difficult to interpret.

[Slide]

Our own studies in vitro have shown that adefovir dipivoxil was not a substrate for cytochrome P450, and, in fact, we looked at the ability of adefovir or adefovir dipivoxil to inhibit the metabolism of the known substrates of the major isoforms of cytochrome p450, including 1A2, 3A4, and 2DT, and we showed that neither compound was an inhibitor. In addition, looking at the metabolism of adefovir dipivoxil in microsomes from rats that had been induced with various compounds inducing 1A2, 2B3A and 4A,

there were no changes in the pharmacokinetics of adefovir.

We also looked at the potential for induction of P450 in rats using adefovir dipivoxil dosed orally, and we saw no induction of the major isoforms. So, on the basis of this data, no pharmacokinetic interaction involving cytochrome p450 would have been expected.

[Slide]

This was the design of our own formal drug interaction study, looking at healthy volunteers in a single dose format. We looked at 6 different drugs, including lelavirdine and saquinavir, and they were studied in a random sequence and in a crossover design with 8 patients per arm.

[Slide]

This shows the effects of adefovir on the levels of saquinavir in our study. This is within patients so it is a crossover design and is using the 60 mg dose of adefovir dipivoxil as opposed to 120 which was used in the ACTG study. There was no significant change in the saquinavir levels.

[Slide]

This slide shows the change in AUC of delavirdine on addition of adefovir in our study. Once again, there was no significant change in delavirdine levels.

[Slide]

One criticism that has been raised is that this is a single-dose study as opposed to multiple dosing. However, this study shows that the pharmacokinetics of adefovir dipivoxil were not changed on repeated dosing for 14 days in HIV-infected patients, demonstrating that there was no induction of a metabolic clearance pathway for adefovir.

DR. BERTINO: I guess one concern I have is that you did this in normal volunteers, not in HIV-infected patients -- your previous slide. Is that correct?

DR. CUNDY: Yes, that is absolutely correct. This study was conducted in healthy volunteers. Our own studies in more than 70 patients, HIV-infected, and more than 80 healthy normal volunteers haven't demonstrated a difference in the pharmacokinetics of adefovir dipivoxil.

DR. BERTINO: I guess my point is that there is data now from Dave Flockhart's group at Georgetown and Angela Kashuba at UNC that shows that HIV patients may be different in terms of pharmacogenetic drug metabolism than normal volunteers. I would also be concerned about the single-dose studies with saquinavir and delavirdine because they are drugs that have dose-dependent kinetics. So, single dose may not be reflective of what steady state might be.

DR. HAMMER: Thank you. Dr. El-Sadr?

DR. EL-SADR: I have a question for Dr. Struble

regarding the safety **data.** It looks like for the 60 mg dose, from your table on page 9, only 73 patients have received that dose for greater than 48 weeks. Right? out of the 73, how many are still on drug?

DR. STRUBLE: Maybe you should address that question to Gilead because I am not quite sure.

DR. EL-SADR: Because if you look at the discontinuation curves below that, it would suggest that -- I don't know -- very few even of those are still on drug after 48 weeks.

DR. STRUBLE: Correct. There were 73 patients that received it for more than 48 weeks at the time that I got the submission. So, at this time I don't know how many more have received the drug for more than 48 weeks, or how many less have received the drug for 48 weeks.

DR. HAMMER: Dr. Jaffe?

DR. JAFFE: Thank you. Just one point of clarification on the pharmacokinetics, we hope to have in the not too distant future, additional pharmacokinetic data on multiple dose from study ACTG 398 where HIV-infected patients received saquinavir and adefovir in combination with other antiretrovirals. We do not have that data, and look forward to having it to clarify some of the issues in the future.

As far as the 73 patients who were part of the NDA

database at 60 mg for greater than or equal to 48 weeks, that is the data we have as of the last data cut-off. However, because of the ramp-up of enrollment on the 60 mg arm on expanded access, we will be having approximately 75-150 additional patients per month to add to the greater than 48-week database. So, each month that we cut the data, we will be having more of those patients available for review.

DR. HAMMER: Thank you. Dr. Stanley?

DR. STANLEY: This is related to that also. I guess I am confused about 417. You show a chart on time to study drug discontinuation for both the 60 mg and 120 mg doses, but then at some point somebody said that at 20 weeks everybody transferred over to the 60 mg dose.

DR. JAFFE: Yes, during the performance of study 417, and well after many patients had been randomized, with the unblinding of study 408 the extent of nephrotoxicity associated with 120 became evident. With that information, our independent DSMB met to review the accumulating database and found that there was similar anti-HIV activity between the two different dose groups. However, there appeared to be more nephrotoxicity in one of the dose groups. So, they felt it was important to have everybody who was presumably on the higher dose, dose reduce at week 16, with the rationale being that the drug appeared to be producing activity, anti-HIV effect, and that more patients would be

able to stay on the drug longer and benefit for a longer period of time.

DR. STANLEY: But on this chart that you showed, even on the 60 mg dose you got a high rate of discontinuation. I mean, only 30 patients lasted 48 weeks.

DR. JAFFE: That is correct.

DR. HAMMER: Dr. Feinberg?

DR. FEINBERG: Thanks. I was trying to get my thoughts together. Let me mention a couple of questions that I have for the sponsor. Study 408 is the only study that appears to be supportive of their proposed indication in treatment experienced patients, at least by statistical criteria by the p-value. It is not clear to me that the small difference in viral load change is a clinically meaningful change.

But I think another issue even in interpreting 408 is, as I recall from our meeting a year ago, patients were also permitted to change -- the protocol asked people to try to remain on stable background therapy but, in fact, patients did, indeed, change their background therapy before the specified clinical endpoint time of 24 weeks. We didn't see any data about what proportion of patients did that, or what was the outcome of those individuals.

DR. JAFFE: Sure. Just one point of clarification, although not presented by FDA and we only

presented the results of one study, there are 2 additional studies which have demonstrated anti-HIV activity. They are both short-term in duration. That is study 402 which enrolled treatment experienced patients and looked at the dose range of 125-500 mg once a day for 2 weeks, and there were statistically significant differences between the placebo group and the active-treated arms. As previously presented, in study 403, patients were dosed 6 weeks during a blinded study and then had rollover to an additional 6 weeks monotherapy versus placebo, and there were clear statistically significant differences between the treatment arms in treatment experienced patients.

[Slide]

DR. TOOLE: In study 408 patients were discouraged from changing their antiretroviral regimen for the first 24 weeks. However, about 20 percent of patients did change and there was no difference between the 2 arms.

[Slide]

We also conducted an analysis where we excluded patients who added a new antiretroviral agent. As shown here, for the active group during the first 24 weeks, for those that did not add an agent, there was still a decrease of about 0.3 logs after 24 weeks. In addition, for those patients who were on the placebo arm and added adefovir during the open-label phase, we also applied the same

analysis and, again, a decrease of about 0.3 logs is observed after 24 weeks.

DR. FEINBERG: I am sorry because that went by very quickly. So, you are saying that this is the viral load change outcome?

DR. TOOLE: This is excluding those patients --

DR. FEINBERG: Excluding those who made a change in the first 24 weeks.

DR. TOOLE: On adefovir, either after rolling over from placebo to the open-label phase of adefovir, or during the blinded period.

DR. FEINBERG: So, do you have a slide looking at that as an intent-to-treat? In other words, the same analysis -- oh, no, it wouldn't be that. I am sorry.

The next concern I have is kind of global. I am not even sure how to phrase it. I guess I am concerned that studies 402, 403 and 420 have never shown any evidence of a dose response with respect to the antiviral activity of adefovir. In addition, at least by your Kaplan-Meier estimates from expanded access, there doesn't seem to be any dose proportionality for nephrotoxicity either.

So, I guess I have questions about why not choose -- I mean, I am trying to figure out why 60 mg is the dose of choice, why that does might not be smaller than 60 mg? I understand that the hepatitis B dose is 30 mg and, given

everyone's concerns about nephrotoxicity, I wonder if you could tell us about the 30 mg database. I understand it is a different disease and a different population but I would like to know is nephrotoxicity evidenced at 24 or 48 weeks of treatment for hepatitis B and, if so, is that onset later in time than you have shown us for 60 mg? I understand we are talking about different indications. My concern is what is it that this drug does, and why is 60 mg the right dose.

DR. TOOLE: As part of our Phase IV commitments we will be investigating the 30 mg dose with regard to anti-HIV activity and safety profile. If I could have slide 62, please?

[Slide]

With regard to the difference between 60 mg and 120 mg observed in study 417, this slide looks at the Kaplan-Meier analysis for the time to onset for serum creatinine increase. In this case, we do see a significant difference, as shown by this p-value, for the development of nephrotoxicity. This is for creatinine increase. We observed the same difference for hypophosphatemia.

DR. FEINBERG: I might remark that on that slide the inflection point in terms of time for both doses, you know, appears to be happening between 24 and 28 weeks.

DR. TOOLE: That is correct. When we began the study we weren't certain whether what you would see is a 2-

fold delay before the development of nephrotoxicity at the lower dose. It is clear that is not the case. However, the apparent plateau does seem to be lower. This plateau was also observed in study 408 even when there was a significant number of patients at risk for the development.

DR. HAMMER: Have you done an analysis if you stratified for a different creatinine level? I am sorry to interrupt, Judith, but if you did greater than 0.3 from baseline, for example, because the time of onset does look the same. The cumulative proportion of patients with nephrotoxicity by that definition is different but I think the group might be interested to see if you used a lower threshold what those curves might look like.

DR. TOOLE: We haven't done that primarily because if you look in study 408, the patients on the placebo arm who had a 0.3 rise is about 15 percent, and for a 0.2 increase it is about 40 percent.

DR. JAFFE: I should also point out that in the expanded access program we were able to compare 1000 patients at 120 mg to 1000 patients at 60 mg with similar lengths of exposure, and while there is an incidence of about 40 percent according to the Kaplan-Meier estimates at a year in the 60 mg group and 50 percent in the 120 mg group, according to the log rank test that is highly statistically significant.

Now, in terms of 30 mg and what we might expect to see, we have now treated about 25 chronically infected patients with HBV at 30 mg for about a year, and we can see at about 10-11 months, now having precise knowledge of what to look for, small up-ticks in creatinine, smaller than the 0.5, associated with minor decreases in phosphate. So, we might expect to see nephrotoxicity associated with the 30 mg dose but at a much lower incidence and delayed onset as well.

DR. FEINBERG: Those are co-infected patients, chronic hep. B and HIV, or just chronic hep. B?

DR. JAFFE: Those are chronic hep. B infected patients without HIV. There have been studies that have looked at co-infected patients as a subset of the CPCRA study 039. About 10 percent of patients were co-infected and, as part of the CPCRA's analysis it appeared that there was less incidence of renal toxicity. Whether or not that is influenced by the small numbers we don't know. As recently presented by the 039 study team, there was clear activity against hepatitis B infection in those patients compared to placebo.

DR. FEINBERG: I have just a couple more sort of follow-up questions, just chasing this issue of the nephrotoxicity. One is that although we have been given a lot of laboratory data, other than one slide which said 6

patients or 1 percent had been reported as having a Fanconi-like syndrome, we really haven't been shown anything about the clinical impact of this nephrotoxicity on patients, and I wonder if you have the data in that format to tell us something about the actual clinical manifestations.

DR. JAFFE: Sure. Much of the serious renal adverse events that were reported were early on in the program where knowledge of the precise manifestations of toxicity were unknown and may have led to hospitalization. That is the slide that Jay presented earlier, which reflected not understanding the pattern of toxicity.

Now, at 60 mg we can say that in the 120 or so patients who came off study drug in the first 1000 patients at 60 mg, 5 of those events were considered to be serious; 2 of those patients underwent hemodialysis. Both were extremely complicated patients with viral loads well above 100,000 copies at baseline, on multiple concomitant medications.

One of the patients had developed pancreatitis and hepatitis, and with a normal creatinine off adefovir was hospitalized and, while in hospital, received IV radiocontrast for an abdominal CT scan and developed renal failure while off adefovir.

The second patient also had a similar background history, developed pancreatitis and, while in hospital, not

receiving IV radiocontrast, had multi-organ failure.

[Slide]

I think it is important to put this a little bit in context. The point of this slide is to show that renal failure can occur with adefovir. This is at 120 mg, and this is one of the two patients from the controlled clinical trials who went on to dialysis. He is a 55-year old African American male who had multiple preexisting medical conditions and was on a slew of other drugs, who came off adefovir after an increase in his creatinine up to 2.4 mg/dL. Over the next month, with evidence of wasting syndrome and a variety of other issues coming up, the patient was hospitalized with renal failure and underwent dialysis and also underwent biopsy. In that biopsy, it was consistent with severe acute tubular necrosis as well as clear evidence of mesangial proliferation, consistent with HIV neuropathy.

The point of this slide though is to show you that while it is quite clear that adefovir is a nephrotoxin, in an advanced AIDS population there will be background noise with regard to renal failure. And, this patient, in the placebo group, is a patient who was hospitalized for the treatment of pneumonia and in hospital received antibiotic therapy and ended up with renal failure.

So, we can state, I think fairly confidently based

on the data, that adefovir is a mild nephrotoxin and that there is, however, background noise in the placebo group of patients who won't receive adefovir. So, it is very difficult to sort out the actual contribution at times of adefovir to the patient's course.

DR. FEINBERG: Thank you. This last bit on nephrotoxicity is directed at the FDA, mindful of what Scott just asked about, looking for smaller increments in creatinine and understanding that creatinine is not an arithmetic test but represents a logarithmic function. If I remember my internal medicine correctly, if you double your creatinine you lose 90 percent of your GFR. So, have you done an analysis that looks at smaller decrements in renal function? I guess what I am saying is I am concerned that a lot of what we have seen this morning, if I remember correctly, seems to be premised on this half milligram change, which is really an enormous, enormous change in the ability of your kidneys to function correctly. I wonder if you have looked at anything less than that.

DR. STRUBLE: No, we haven't. We have only looked at 0.5 mg/dL increase from baseline for serum creatinine because that was the definition that was given to us for the development of this nephrotoxicity.

DR. HAMMER: Thank you. Dr. Mathews?

DR. MATHEWS: I would like to ask two questions at

this time. One relates to the 30 mg dose that is possibly recommended for toxicity in the package insert. The other is related to what is known about potential mitochondrial toxicity.

So, with regard to the 30 mg dose, the package insert has guidelines for dose reduction that include that dose, but I am wondering, since we haven't heard any data on the efficacy of that dose, whether there is a rationale for using it as opposed to withdrawing the drug altogether.

[Slide]

DR. TOOLE: In studies 411 and 417 42 patients were dose reduced primarily for nephrotoxicity. Looking at their median change from baseline following the dose reduction shows little evidence of rebound after 16 weeks.

DR. HAMMER: Could I ask a follow up? Do you have data when you stopped the drug completely, the same curve, either in this study or other studies? When adefovir is stopped completely is there an RNA rebound?

DR. TOOLE: We don't have data from this study for that, no.

DR. HAMMER: Do you have any data, because I think it relates to Dr. Mathews' point?

DR. TOOLE: In study 408 we have seen a return towards baseline in patients, but there are very few patients in that study who don't go onto other regimens

after discontinuing adefovir so the numbers are small. I am sorry, what was the second part of your question?

DR. MATHEWS: To summarize, I mean, since these people were on background therapy we don't know, in fact, that failure to rebound is due to the fact that the 30 mg dose is active or that there is background activity in the regimen that they were on. Is that correct?

DR. TOOLE: That is true, but I think at least in study 411 the efficacy data are fairly convincing that the S-drug regimens with adefovir have activity which is comparable to the control.

DR. MATHEWS: I understand that, but at this dose level, that is the question. And, a lot of people would be exposed to that dose level in therapy.

The next question I have relates to whether in vitro studies have been done to assess the potential mitochondrial toxicity of this agent. In particular, I think it is interesting because of the carnitine depletion that accompanies use of this agent.

DR. TOOLE: Yes, we do have in vitro studies regarding inhibition of polymerase gamma.

DR. BISCHOFBERGER: We don't have any evidence from preclinical studies, including animal studies and woodchuck studies, that there is any mitochondrial toxicity.

[Slide]

We have looked at inhibition of human polymerases, including the mitochondrial gamma polymerase. Shown here is the kinetic substrate specificity. So, in terms of the natural substrate, 100 percent would mean it is as efficient as a substrate as deoxy NTPs. As you see here, the best substrate in this study was ddC with 25 percent deficiency. The next one was ddA-TP with 20 percent; the next one, D4T; then came adefovir diphosphate and then 3TC. So, in summary, there is a substrate for gamma polymerases but at less efficiency than ddC, ddI, and D4T.

DR. HAMMER: Can I just ask for a clarification to understand this, AZT triphosphate is **a** mitochondrial toxin but in this assay there is no incorporation?

DR. BISCHOFBERGER: We did not see any incorporation in this assay, but if I can show slide 1143 --

[Slide]

What we have done here is we have just measured Ki's rather than efficiency of incorporation. Here, AZT is included. You see gamma polymerase. It has a Ki of 18. So, the higher the Ki, the lower the inhibitory -- so AZT is 18; adefovir phosphate, in this case, is 0.97; ddC is 0.034. Dr. Hammer, does this answer your question?

DR. HAMMER: Yes.

DR. BISCHOFBERGER: Thank you.

DR. HAMMER: Dr. Yogev?

DR. YOGEV: Well, I have about 24 questions so let me start.

DR. HAMMER: Stop with 3 and we will come back to the other 21 later.

DR. YOGEV: The first question I have is basically for the team at the FDA. Do we accept the 0.3 log as a real reduction? Is 0.3 meaningful to even consider this drug as really an addition to the armamentarium? Maybe I was spoiled with the NNRTI and protease inhibitors. So, I wonder how my colleagues feel about it.

The question to the company is, ddI, I noticed, **was** one of the few which was 29 percent increase -- is ddI going to be excluded from the armamentarium? Any recommendation for that because now many of us are using hydroxyurea which increases even more the intracellular -- are we going to see more pancreatitis because of combination with this drug? Are there any data for the ddI accumulation?

DR. JAFFE: I can't answer the first question for the FDA. So, I would invite one of them to come up and deal with that if they would like, but in terms of ddI-related side effects, we have long-term placebo control from study 039, and the incidence of the primary ddI side effects, peripheral neuropathy and pancreatitis in both cases is higher in the placebo group compared to the active group,

the adefovir-containing group. The use of ddI at baseline is roughly similar. So, there is no data to suggest at this point in time that these minor elevations that we saw in the single-dose study have any clinical relevance.

DR. YOGEV: But those data are only for the first 20 weeks.

DR. JAFFE: No, no, this was the long-term placebo-controlled trial where patients had a median follow-up time of 11 months on study.

DR. YOGEV: I am a pediatrician and I almost feel that I don't belong in this session because you didn't present any data on pediatrics and, yet, in the insert you are claiming that maybe it can be used between 4 months and 18 years. Can we see a bit more data on that?

[Slide]

DR. TOOLE: We conducted study 418, which was an open-label, dose escalation study at 2 dose levels of adefovir, either 1.5 mg/kg or 3 mg/kg, in combination with other nucleosides and nelfinavir. There were 25 patients in this study. These were HIV-infected children who were nelfinavir-naive, with HIV RNA greater than 400 copies/ml. The duration of the study was 16 weeks for the primary phase, followed by an open-ended extension. The endpoints of the study were PK, safety and HIV RNA changes.

[Slide]

The objectives of the study were to establish an appropriate dose of adefovir dipivoxil in children; to evaluate the pharmacokinetics, safety and tolerance of adefovir at 2 dose levels in combination with other antiretrovirals; to evaluate the antiretroviral response through 16 weeks of treatment, as well as to obtain preliminary information on the potential interaction of adefovir and nelfinavir.

[Slide]

The children received adefovir in a suspension formulation which was dissolved adefovir in combination with L-carnitine in a sweetening suspending vehicle.

[Slide]

The baseline demographics show the mean age of the children to be about 6.5 years, primarily girls, with a mean HIV RNA of about 80,000 and a mean CD4 percent of about 25 percent.

[Slide]

Adefovir dipivoxil was well tolerated as all children completed 16 weeks of treatment. Three patients discontinued for an adverse event and all three of these were due to hypophosphatemia which, again, developed in the extension phase, that is, beyond 16 weeks.

[Slide]

This slide summarizes the grade 3 or higher

adverse events observed during the study. There were no grade 1 adverse events. There were 3 grade 3 adverse events, neutropenia, a congenital anomaly which was diagnosed during the study, and 2 case of hypophosphatemia at the higher dose level.

[Slide]

These children gained weight and height, as shown here. This is looking at the mean change in weight and height at week 24. However, when looking at the adjusted Z-score, which is an instrument to take into account the patient's age and gender, the children were relatively underweight for their age with a Z-score of minus 0.2. However, it is important to note that these children came into the study with a Z-score of minus 0.35.

[Slide]

The study was conducted with adefovir being added onto background therapy for a l-week lead-in and then nelfinavir was added on day 8 and continued. After week 1 for both dose levels we observe about a 0.2 log decrease, with a range of minus 0.5 to plus 0.4. At week 16, after the addition of nelfinavir, there is a 0.5 decrease from baseline, with a range from minus 2 to plus 8.

[Slide]

So, to conclude, adefovir in combination with nelfinavir and other NRTIs has been well tolerated. The

median duration of adefovir for this study is 80 weeks. Adefovir at the 1.5 mg/kg dose provides similar exposure to the 60 mg dose used in adults, and based on trough and peak levels of nelfinavir there is no apparent interaction.

DR. JAFFE: Since we seemed to have skipped past the issue of the magnitude of the viral load change to pediatrics, I thought it would be useful to just take this opportunity and put a 0.3 log change into some proper context. This is looking at monotherapy studies of other nucleoside reverse transcriptase inhibitors. These are not our data. They come from an ACTG study which has been presented publicly, and the Merck 033 study which may still be in their package insert.

[Slide]

This is a study in patients who had received AZT monotherapy. It was a complicated study design which I believe had 4 arms associated with it, but 2 of the arms had patients rolling over to either D4T or ddI monotherapy. As you can see, here the viral load declines over time, for D4T by week 24 probably about 0.125 and at the end of 48 weeks it is above baseline. For ddI the activity is clearly greater, but at the end of 48 weeks approximates about 0.4 to 0.5. That is in treatment experienced patients.

[Slide]

Now we are looking at treatment naive patients

here. This is the study design. Treatment naive patients were randomized either to zidovudine alone, indinavir alone or zidovudine plus indinavir.

[Slide]

You can see that AZT in the treatment naive population through 24 weeks has about a 0.3 to 0.4 log decline. So, I think it is important to put the changes we have seen with adefovir in context. It is also important I think to understand how treatment effects may differ according to the treatment population that you look at.

For example, if we were to focus here on this treatment naive group and look at the combination of AZT and indinavir, which is about 1 log or 90 percent of the virus in your blood, if we were now to extrapolate to study 411 and look at the results that we see in the triple control, AZT, 3TC and indinavir, I think we can confidently say that 3TC is supplying about another 0.6 log decline. The mean change at week 20 in that study is about minus 1.6. However, if we feel confident in making that extrapolation, I think we also must acknowledge that given the results that we have seen with the triples including adefovir, that adefovir is supplying the same 0.6 treatment effect in that treatment naive population.

DR. YOGEV: Well, the study you presented, it was from 1.9 to 12.9 age, yet you are claiming it to 0.4. That

supposes it can be used at less than 2 years of age. We know from multiple studies that the pharmacokinetics in the younger ones is so much different that I was just wondering where you got the 4 months of age into that group, suggesting that it can work.

Also, it is interesting that the variation in that specific group that you are reporting, for the **area** under the curve the standard deviation from 1.29 is almost 0.3 mcg/mL, which is more than double what is in the adults, suggesting that there is going to be a huge variation in that population. Shouldn't you just limit yourself to the 2 years and older unless you have a PK which you didn't show us to show the same? Also, try and explain to me why you can go to 0.75 on toxicity.

DR. JAFFE: There is very limited information in terms of dose reduction, and your comments regarding the age threshold are well taken. Dr. Cundy will present some of the pharmacokinetic information.

[Slide]

DR. CUNDY: This slide compares the pharmacokinetic data obtained in 10 HIV-infected children, at the dose of 1.5 mg/kg of adefovir dipivoxil administered as a suspension of the tablets, with data for the 60 mg dose in HIV-infected adults.

As you can see, the AUC and the Cmax under these

conditions are almost identical. This also demonstrates, however, that the apparent clearance of adefovir in children is somewhat greater than it is in adults. But one would expect that a 1.5 mg/kg dose would administer a similar exposure of adefovir to a 60 mg dose in adults.

[Slide]

This is a graph that shows the effect of age in the cohort of HIV-infected children on the apparent bioavailability of adefovir dipivoxil, and there is no demonstrated relationship with age, illustrating that we got very similar bioavailability across the range of 2-10 years of age.

DR. YOGEV: You just reconfirmed what I am asking for. Less than 2 years of age, do you have any data? I have no problems with 2 years and above. I am talking about less than 2 because you are suggesting that it can be used in 6 months of age.

DR. CUNDY: There was a previous study conduct ed, study 406, in HIV-infected children where some pharmacokinetic data was generated at ages below the 2 year limit that was --

DR. YOGEV: Sorry for interrupting, but that specific study was on 8 patients and the range was from 0.4 to 17 years of age. One would like to know how many were really tested at less than 2 years to justify usage of this

drug.

DR. CUNDY: Yes, as far as the clinical outcome for 406, I will leave that up to Dr. Jaffe.

DR. JOLSON: Scott, I wonder if I could just interject something as a point of clarification?

DR. HAMMER: Sure.

DR. JOLSON: I mean, as Dr. Yogev pointed out, normally we would have presented and commented on the pediatric information as part of this NDA, but as a point of clarification it is probably worth mentioning that the pediatric formulation has only recently been submitted. It is part of a separate NDA, and that is why you are not hearing our commentary on it. I think it has only been in-louse for about a month or so. Gilead can correct me if that is incorrect. So, we will take your comments under advisement, but that may be why you haven't heard a more proactive approach toward viewing the pediatric information from our side.

DR. YOGEV: So, that suggests that in our discussion we are discussing we are only discussing potential approval, or advising for approval, for adults only, excluding pediatric?

DR. JOLSON: That is correct. The NDA that we are talking about today is for the adult indication. The comments that you are making now will be relevant to the

pediatric indication but that is not part of today's application. They were separated in time by many months, about five months.

DR. YOGEV: Does that also include pregnant women?

DR. JOLSON: In terms of? What would your question be?

DR. YOGEV: Because now we are going to approve it for adults and I didn't see any data on pregnant women. There was no discussion of that, Are they going to be excluded? Because the way it is written in the insert is in certain cases this drug can be used, and I am not sure we saw any data for safety pharmacokinetics to suggest 60 is right.

DR. JOLSON: Well, I would ask the sponsor to respond to the experience in that population, but also it is probably worth mentioning that the draft insert that you see is what was submitted with the application. Normally, by the time a product gets to market the insert has undergone substantial revisions. So, anything is fair game for comments, but you shouldn't look at anything as though it is locked in.

Just getting back to the original question about the relevance of viral load, maybe Dr. Murray can just comment about our division's approach to that issue.

DR. MURRAY: Well, it is true what you said for an

individual for two separate HIV RNA measurements. The variability could be 0.5 to 0.7 logs, but when you are looking at a large number of patients in a clinical trial smaller differences than the variability from one individual can be relevant.

I think two years ago we couldn't tease out what the lowest threshold would be for an HIV RNA reduction still having clinical benefit. I mean, when we looked through a lot of the clinical endpoint studies, the majority of studies were an incremental 0.3 log or greater reduction seen was associated with clinical benefit. It seemed like though that somewhere below 0.3 logs it was plus or minus. In some studies clinical benefit followed and in others it didn't. You have to remember that there is a lot of difficulty because what a drug can do as monotherapy might be very separate from what it does when it is being used in an active combination. There probably is synergy, and it depends -- you know, some of the viral load reduction is all up front, if it is transient, all in the first 8 weeks -- you know, a viral load reduction even greater than that but if it is not sustained would probably not give you clinical benefit. So, it is a bit complicated question, but something below the inter-subject variability probably -- the variability from one subject probably does confer clinical benefit.

DR. HAMMER: Thank you. Dr. Hamilton?

DR. HAMILTON: Expanding somewhat on the topic we are talking around at this moment, I would like to tilt a /little further toward that clinical windmill and inquire as to whether, in fact, the projection illustrated in this analysis of the relationship between the clinical disease progression and changes in HIV RNA have, in fact, been evaluated at all in the conduct of the course of the studies of what must be several thousand patients now. Recognizing that clinical endpoints has not been, at the outset, the subject or the statistical focus of these studies, nonetheless, I would have hoped that some data might, in fact, have been collected. I notice in the safety profile slide that Dr. Jaffe just showed that there were, in fact, 16 or 17 deaths in 2 treatment arms, only 1 of whom died apparently of renal failure. I would kind of like to know what they did die of. Are there morbidity, mortality, quality of life measures that we can use to help validate the putative benefits of this modest reduction in viral load?

DR. JAFFE: By the way, we have not tested, nor have any information in pregnant women.

[Slide]

This looks at the mortality in 039 and, as Dr. Toole indicated earlier, the real value of this study is

having a long-term placebo control. In the absence of a long-term placebo control, 24-week studies per se, particularly with patients who may have higher CD4 cell counts, it is very, very difficult to assess, because of the low event rate, what impact your drug may have.

The primary endpoint of this study was survival and, as you can see, there were 17 deaths in the adefovir group, 16 in the placebo group, and there are numerous different reasons. I should point out that 1 patient who had an arrhythmia was on the adefovir arm but died 5 days into study, never having received study drug. So, the distribution, or at least the numbers, is quite similar.

[Slide]

Looking at some of the other secondary endpoints, we can see that there is no difference with regard to death, 17 versus 16. With regard to CMV disease, and because of the demonstration preclinically and to some degree in an early clinical study of anti-CMV activity, this study actually had nested within it a CMV prophylaxis study. So, patients were actually screened at baseline to make sure that they did not have CMV retinitis. But similar to the changes in terms of mortality events, the decrease in CMV retinitis was also impacted by the changing background HIV therapies. There were 5 patients on the adefovir arm compared to 10 on placebo that had CMV.

If we now look at progression of disease including death, there were 40 on the active arm compared to 48 and none of these achieved statistical significance.

[Slide]

Now, if we look a little more carefully at some of the clinical endpoints, these are data that have just recently been received by Gilead. We have not had a chance to analyze them, nor has the FDA. We are now looking at first occurrence of specific opportunistic disease, now looking at PCP, candidiasis, confirmed CMV, wasting syndrome, age-related malignancies, other OIs, and in this grouping we are talking about herpes zoster, Microsparidia, a variety of other endpoints and AIDS dementia complex or PML, there are 39 first occurrences in the adefovir group compared to 62 in the placebo group, and this achieves statistical significance. This is our p-value. This has not been done by the CPCRA, and it is an unadjusted analysis for baseline CD4 and RNA. So, there is some degree of evidence of differences between the two groups.

DR. HAMMER: Is that invasive esophageal candidiasis or is that oral candidiasis?

DR. JAFFE: We don't have that information, but we have reasons to believe that it is oral, esophageal and perhaps even disseminated.

DR. HAMMER: And, was prophylaxis comparable

between the two groups, for example, for the PCP?

DR. JAFFE: Yes, it was.

DR. HAMMER: Those data are driven by PCP and candidiasis. So, I think one has to really look at those two categories quite carefully.

DR. STANLEY: Dr. Hammer, we should also point out that in this study there was no virologic benefit shown with adefovir.

DR. HAMMER: Dr. Masur?

DR. MASUR: In order to understand the nephrotoxicity a little bit better, could you elaborate on either preclinical or clinical data about what the mechanism might be, and also on the same issue, obviously you have looked at doses between 30 and 250 or 500. What evidence do you have either preclinically or clinically that this nephrotoxicity is, in fact, dose related?

DR. TOOLE: Preclinically, on histological examination we observed only a tubolopathy, glomerular changes. The tubolopathy was not accompanied by any changes in serum chemistries of creatinine or phosphorus. We did observe very minor changes of keriomegaly at doses as low as 1 mg/kg/day.

DR. MASUR: That is pathology. Do you have any indication of what the pathophysiology of this is? Why is this unique to this particular class of compounds or this

compound?

DR. TOOLE: I was going to address the mechanism of nephrotoxicity.

[Slide]

We have recently cloned and expressed the human organic anion transporter from human kidney, and found adefovir to be a substrate. The human organic anion transporter has been shown by immunohistochemistry to be localized to the proximal tubules. Based on that, shown here is a model for a proximal tubule cell. We believe that adefovir is transported to the proximal tubule cell by the organic anion transporter, and through an unknown mechanism is also secreted into the glomerular filtrate. Over time, either adefovir or metabolite accumulates and through an unknown mechanism leads to cellular injury. After injury, transport re-uptake from the glomerular filtrate of glucose and phosphate is inhibited, resulting in glycosuria and hypophosphatemia. Inhibition of protein uptake is inhibited, resulting in proteinuria, as well as inhibition of secretion of hydrogen ions which result in reduced serum bicarbonate.

DR. HAMMER: Could I just ask what hydroxyurea does, does it potentiate the toxicity either clinically or at your basic mechanistic level?

DR. TOOLE: We don't know in terms of a basic

mechanistic level. In our expanded access program we have done a preliminary analysis looking at patients who have received hydroxyurea. There has been no increase in associated nephrotoxicity in those patients.

DR. BENDELE: I am Ray Bendele, Gilead Sciences. We do see a dose-related increase in nephrotoxicity in animals, in that in the rat, at approximately 100 mg/kg, we do begin to see increases in BUN and creatinine, as well as histologic changes. As we increase the dose in monkeys orally, we have never seen increases in BUN and creatinine even at 75 mg/kg for 30 days, or 25 mg/kg for 3 months. But if you give a high enough dose intravenously in the monkey you can produce proximal renal tubular necrosis.

DR. MASUR: So, are you suggesting that there is a threshold at which you get toxicity? Do you have any data suggesting that as you augment the dose you get earlier or more severe or less reversible toxicity?

DR. BENDELE: No, as you increase the dose in the rat, for instance, at 37 mg/kg in some of the studies that we have run for up to a month, we don't see any evidence of increases in chemical chemistries, BUNs or creatinines, although we do see some histologic evidence of renal toxicity. As we increase to 100 mg/kg we do see more severe renal toxicity with increases in BUN and creatinine.

In terms of the histologic effect, the longer the

duration of treatment in the rat, for instance, the lower the dose at which you see the cytomegaly in the kidney, but it doesn't increase in severity as you increase the duration of exposure. And, the effects are reversible. In the monkey after 20 weeks at 25 mg/kg there were 7/8 animals at that had the histologic change of keriomegaly. After a 1-month recovery only 1/8 animals had any evidence of keriomegaly. So, we do see recovery of the histologic lesion. Although not totally, we do see recovery after 1 month in the monkey.

DR. HAMMER: Dr. Lipsky?

DR. LIPSKY: First a question on efficacy and then another one on kinetics. In the expanded study you reported that by 9 months approximately 50 percent of the patients were off the drug. Nephrotoxicity was only about 17 percent. Why are people stopping the drug? Is it efficacy? Toxicity? What is going on?

DR. JAFFE: In this patient population it, no doubt, is a combination of various factors. In the expanded access program, in a setting where data are not audited, we are left with what the physician sends in, in the case report forms. So, in terms of the 50 or so percent that have come off, about 20 percent come off for adverse events; about 10 percent come off for progression of AIDS; 2 percent have died; and then there are various other reasons,

including non-compliance, loss to follow-up, etc.

DR. LIPSKY: I see. Thank you. On the kinetics of the drug, when you did the dose reduction down to 60 mg, in the brochure that you presented, with an N of 6, you achieved a Cmax of around 0.1 mcg/mL, which appeared to be virtually identical to the Cmax at 120 in I think the 402 study, the one that you gave us, the reprint published in JID. Is that because of a difference in assays or how does the concentration respond to the dose?

[Slide]

DR. CUNDY: This is now looking at the data we have comparing short-term dosing of adefovir dipivoxil with long-term dosing in a limited number of patients. Here we nave comparisons of 12 patients that had long-term dosing and 6 further patients that had been dose reduced for nephrotoxicity. You can see here the apparent clearance of adefovir was reduced somewhat upon long-term dosing in all patients. However, it was further reduced by about 55 percent from control values in patients that had actually been dose reduced for nephrotoxicity.

DR. LIPSKY: No, just classic pharmacokinetics with this drug -- what is the relationship between the dose you give and the level you get?

DR. CUNDY: Oh, okay, I understand the question.

[Slide]

This slide demonstrates the dose proportionality of the Cmax of adefovir following oral dosing of the dose range from 60 mg up to 500 mg.

DR. LIPSKY: And that was what? Normals?

DR. CUNDY: This is all HIV-infected patients.

[Slide]

This is a similar **graph** for AUC values in HIV-infected patients over the same dose **range.**

DR. LIPSKY: Then, dose related to effect, the curves are very flat. Is there any information about cellular uptake of this drug?

DR. CUNDY: We don't currently have **an** analytical method that is capable of measuring intracellular levels of adefovir, although we **are** looking right now at finding a more sensitive method with the hope of being able to do that.

DR. LIPSKY: In the information you gave you said intracellular levels had a half-life of about 30 hours.

DR. CUNDY: Those were actually based on studies in resting and activated human PBMCs using radiolabeled drug.

DR. LIPSKY: I see. Thank you.

DR. BISCHOFBERGER: Can I clarify something very briefly? We have actually carried out an analysis of intracellular levels in monkeys. Could I have slide 1150?

[Slide]

This shows a study we have done with C14 labeled adefovir. We have looked at plasma levels and intracellular levels of both adefovir and the antiretroviral active metabolite. As you see, the plasma half-life is on the order of 5-7 hours, and the intracellular half-life is very long. It is on the order of 30 hours. We don't have the corresponding data in humans, but this is in monkeys.

DR. HAMMER: Is there a dose response in the diphosphate levels? That would help us enormously, I think.

DR. BISCHOFBERGER: Yes, we have actually gone from 15 mg/kg in the monkey up to 60 mg/kg and safety and efficacy see very nice dose proportionality, 4-fold higher intracellular levels. It correlates to the plasma AUC.

DR. LIPSKY: What is your interpretation of the flat dose-response curve?

DR. BISCHOFBERGER: I am sorry, which flat dose-response curve?

DR. LIPSKY: In other words, regardless of what dose you have given, you seem to get the same response, whether it is 60 mg, 120 mg, 500 mg and you are proposing potentially 30 mg. Do you have any explanation for that?

DR. BISCHOFBERGER: No, I don't, but I do not think it would be the limitation in terms of intracellular active metabolites. But, you know, one possibility could be

we don't really know where these active metabolites are -- I mean, I am making it up obviously.

[Laughter]

DR. LIPSKY: And, there doesn't appear to be any role for therapeutic monitoring for efficacy or toxicity in this drug?

DR. BISCHOFBERGER: I am sorry, could you say that again?

DR. LIPSKY: Is there any role -- there has been no presentation or any concern, is there any role for therapeutic monitoring for either efficacy or toxicity with this drug?

DR. CUNDY: Actually, we are going to be looking at longitudinal changes in pharmacokinetics in our ongoing study 415, with the idea of seeing whether pharmacokinetics in any way indicate a patient might be predisposed to nephrotoxicity, but we don't currently have that data.

DR. HAMMER: Thank you. Dr. Pomerantz?

DR. POMERANTZ: Yes, a couple of questions on some of the resistance data and the clinical virology. First, maybe Dr. Bischofberger would be the person to talk about this, I am not sure. But I am not sure how the definitions for phenotypic resistance were determined. A variety of studies that I am somewhat familiar with that have been printed recently have had trouble determining what is

phenotypic resistance. And, at one point you talk about high-level AZT resistance as being 8-fold, increased over, I assume, over the non-resistant control, as well as for the ADV in one study, a 4.5 versus a 1.5 was considered a significant increase. Comments, and how you came up with this?

DR. BISCHOFBERGER: Yes. Could I have slide 978?

[Slide]

Shown here is our own data to justify the genotypic definition of low-level and high-level AZT resistance. As you see, if you have single mutations, like 41, 67, 72, 219 or double combinations, 67/70, in general you see less than 8-fold --

DR. POMERANTZ: No, no, I understand that. My question was why did you pick 8-fold versus lo-fold, as one group does, versus 3- or 4-fold, which another group does to determine resistance? Why 8-fold?

DR. BISCHOFBERGER: In the phenotypic analysis which I presented, the 8-fold was actually picked by the company which carried out the analysis, which was Virologic. They felt that 8-fold was the cut-off in their mind for low level or high level.

DR. POMERANTZ: And, do you know, in their mind, how they determined that there was any clinical difference between 8-fold or 7-fold or 4-fold or lo-fold?

DR. BISCHOFBERGER: I am not sure about that. Maybe Brendon Larder can comment on that.

DR. HAMMER: I don't know that Brendon wants to comment on the Virologic cut-offs. But let me just clarify, I don't think that is really Virologic's definition of high-level resistance. That is their definition of clear-cut decrease in susceptibility from their control in vitro. Between 2.5 and 8-fold is a less clear-cut range. So, one can infer from that it is higher level resistance, but I think Virologic is stating that that is a more clear-cut cut-off in determining a change in susceptibility from the control.

DR. POMERANTZ: Then, the second question is that one of your graphs shows that 1.45 versus 1.5 phenotypic difference in ADV resistance was considered significant. Do you think that means anything if you are using 8-fold for the AZT cut-off?

DR. BISCHOFBERGER: In which presentation was that?

DR. POMERANTZ: I don't know the slide number but I have it here, in which high-level AZT plus/minus 3TC -- you have a graph that shows ADV 4-fold resistance versus high-level AZT plus 3TC.

DR. BISCHOFBERGER: Yes, I apologize.

[Slide]

So, these are Virco data, and what in general is observed if you do assays with XTD or NTT as the endpoint you get a bigger spread in the readout, whereas in assays that include light as the readout the thing is more compressed.

DR. POMERANTZ: Right.

DR. BISCHOFBERGER: So, this is statistically significantly different according to Virco.

DR. POMERANTZ: Oh, so this was not Virologic?

DR. BISCHOFBERGER: No, this is Virco data. We have done statistical comparisons between these two and there is a statistically significant p-value associated with the difference between these two.

DR. POMERANTZ: Thank you. That is helpful. The other question I would have is that we have seen some data with less than 400 as a cut-off. Have you looked at any of these studies for less than 50 comparing the different trials with or without ADV?

DR. TOOLE: We did that for both studies 411 and 417 retrospectively. So, not all samples were available.

[Slide]

Shown here are the 3 different treatment groups for study 417. They all have a comparable percentage of patients that were less than 50 using the ultrasensitive assay.

DR. POMERANTZ: Right, and do you have it compared to one of your arms without ADV? There was another study in which you compared it with AZT --

DR. TOOLE: Study 411 --

DR. POMERANTZ: Right. Do you have that data?

DR. TOOLE: Actually, no, we don't but the percentages were again similar for all treatment groups.

DR. POMERANTZ: Similar at what level?

DR. TOOLE: Around 60 percent.

DR. POMERANTZ: Around 60 percent? Wait a second, so you have 60 percent that are less than 50. How many did you have in that trial that were less than 400? They were almost all less than 50 then?

DR. TOOLE: Oh, we do have it.

DR. POMERANTZ: You do?

[Slide]

DR. TOOLE: So, 60 percent is correct in some of the arms, but the control group is 73 percent. The 3 adefovir-containing groups range from 64-71 percent, and the quadruple-containing regimen is 64 percent.

DR. POMERANTZ: And the less 400 put next to those is what?

[Slide]

DR. TOOLE: So, using the intent-to-treat analysis, 59 percent and 50-70 percent.

DR. HAMMER: Is this because the samples -- you said for the other study not everything was available. Is there a selection issue in the samples you had available for culture sensitive testing?

DR. TOOLE: No, just because it was done retrospectively not every sample which was less than 400 was available for reanalysis.

DR. POMERANTZ: All right. I will leave it at that for the time being.

DR. HAMMER: Thank you. Dr. Wong?

DR. WONG: I think we have gotten a pretty good -- you know, as we have listened to the questions and the answers I have gotten a pretty good handle on toxicity and virology. But I guess in my mind the critical issue is still whether 60 mg of adefovir per day is as effective as 120 mg. As I read the briefing book and the results, and then I heard the presentation by Dr. Soon, I had my doubts about using the equivalence design in which adefovir was added simultaneously with two other highly active drugs. I guess I would like to hear the company's response to the criticism or to the concern about whether one can tease out the effect of the lower dose of adefovir when it is given simultaneously with two other highly active drugs, and whether this equivalence design might just be demonstrating the equivalence of no effect versus no effect.

DR. JAFFE: First, we start with the premise that there is clear demonstration of antiviral activity for the 120 mg dose. That is, study 402, 403, 408 all have very similar viral load curves when you give the patient as monotherapy either to no background therapy or to failing background therapy -- they are extremely consistent.

So, now we ask the question how do these results compare to other populations that have been treated? Can we take a look at the results of 417 and understand or have confidence that this is what we would expect to see with three drugs used in a similar patient population?

Fortunately, because of groups like the ACTG and various other groups, there were contemporaneous studies being performed while we were doing 417 that had very similar study designs and treatment populations and, in particular, in protease inhibitor-naive patients.

[Slide]

This is from ACTG 364, and what we are going to do here is focus in on a particular subgroup. Many of you will be aware that this was a randomized comparison of the safety and efficacy of nelfinavir and/or efavirenz with 1 or 2 new NRTIs in NRTI treatment experienced patients. So, it ended up being a 3-arm study: nelfinavir, efavirenz and 2 nukes, efavirenz and 2 nukes and nelfinavir and 2 nukes. Varied within this study is a subgroup that allows us to make

cross-study comparisons to 417, with the caveats that these patients may not have had the same treatment experience as the patients on 417. We do not know the background of 364 virology to be able to make comments. However, these were NRTI-experienced patients, PI and NNRTI therapy naive, and they had viral load greater than 500.

On study 417 patients had to have had a viral load greater than 5000. So we are going to limit the comparison to patients on 364 in the nelfinavir and 2 nuke arm to those patients who had viral loads of greater than 5000. So, here are all of the patients, 66. The baseline is 10,000 copies. However, for the patients with greater than 5000 copies, 39, over half, the baseline is about 30,000.

[Slide]

Now looking at slide 25, this is an analysis done by Gilead, and we are thankful that the ACTG was able to share this data with us. Looking at the patients with nelfinavir and 2 NRTIs, baseline greater than 5000, and looking at their viral load curve over time, you can see that there is an immediate drop with an apparent increase, with about a 1 log difference from baseline at week 24.

[Slide]

Now we are looking at the comparable groups in terms of nelfinavir as the protease inhibitor backbone, adefovir and one other nuke from study 417. The 60 group is

in violet; the 120 group is in light blue. You can see, at the end of 20 weeks that the difference is about 1.2 logs.

Now, we have to be careful because we don't know the exact treatment backgrounds of patients on 364, but we can see from this, the difference being 1 log in 364 and 1.2 log in this study, that we are at the very least in the same ball park.

[Slide]

There are other data that we can look at as well. These are data that appear in the in amprenavir, recently approved protease inhibitor. It appears in the package insert, and this is study PROAB 3006. So, we are simply providing data from the package insert. We do not have any further data to look at. This was a randomized, open-label study. Patients were randomized to amprenavir plus two nucleoside RTIs versus indinavir plus two nucleoside RTIs and, similar to the patients in 364, similar to the patients in 417, these were NRTI-experienced patients who were PI naive. There were 254 patients in the amprenavir arm.

[Slide]

The median age at baseline was 37 years, 80 percent male. The median CD4 count is 399, so somewhat greater than the median cell count in the 417 study and, notably, the median RNA is slightly less than 10,000 copies. The median viral load in the 417 study was, once again,

30,000 copies.

[Slide]

Now looking at a comparison of efficacy across these two studies, and mindful of the clear differences in baseline viral load between the two different groups, 4.5 versus 3.93, the percent less than 400 at week 20 for the relevant comparator arms from 417, adefovir 60 mg plus PI, either nelfinavir or saquinavir plus a nucleoside compared to amprenavir plus two nucleosides is 41 percent versus 43 percent.

So, the point of this is that between these different studies we can gain some degree of confidence that the results are similar from study to study, with the important caveats of not knowing the specific drug treatment histories, with the potential in 364 that they may have been somewhat more drug experienced, but the potential in the amprenavir study that they may have been somewhat less drug experienced.

DR. WONG: But I guess we still don't see with and without adefovir. So, the possibility that all or almost all the effect in the triple combination therapy was due to the other two drugs is still present in my mind. What is your response to that possibility?

[Slide]

DR. TOOLE: Getting back to the activity of the 60

mg dose, I would refer back to study 420 which was a randomized comparison with a placebo control, consistent with what we observed in our other studies, 402 and 403, we again see statistically significant activity, with about a 0.3 log increase after 4 weeks. The DAVG4 was also minus 0.3 logs. Based on the non-overlap of the 95 percent confidence intervals, this is significant, again, demonstrating that the 60 mg dose does have activity.

In our earlier studies we also showed that the treatment effect was similar in treatment naive or treatment experienced patients.

DR. HAMMER: Dr. Verter?

DR. VERTER: I guess I should preface this by letting everyone know that of all the members of the panel, I am the least competent in HIV research, however, I think I have a fairly good knowledge of clinical trial research so I am going to limit my remarks to that, and I apologize if some of the comments are obvious to the rest of the members of the panel, and I will limit it to two of the many questions I have.

My concern comes in the design of the studies and how we can interpret them and, as a couple of other members of the panel have mentioned, the issue of some of the missing data. From my perspective, there are two key trials, 408 and 417, and the comments I have are related to

those. This may be, again, obvious to most people but it isn't to me, that the key is if 408, which was the 120 placebo trial, is accepted as a given that in that type of cohort the effect that was seen is an acceptable effect for approval, although I know they are not asking for approval, that is an important issue. It is almost clear to me that we have accepted that, but not absolutely.

However, even if that is true, the patients in 417 and the design in 417 seems to me to be totally different, and I don't know what impact that should have on our deliberations. If we accept 408, does that mean that even though the entry criteria and the cohort risk level of the 417 patients is not as relevant? For example, if I am interpreting all the slides I have seen today plus what was in the package correctly, in 408 at 24 weeks the percent of less than 400 copies was about 8 percent in ADV and 4 percent in placebo, whereas in 417, the 120 response rate was 31-45 percent depending on which type of analyses you did, and with 60 it was 41-48 percent which, to me, suggests that there is something different between those two cohorts and that may or may not impact on the comparison of 60 and 120. so, that is my first issue on the risk level differences, including prior exposure to drugs, both the type and the length, as well as the RNA and CD4 differences.

Can I ask one more and then I will save the rest

for later?

DR. HAMMER: Oh, sure.

DR. VERTER: Then, as important to me is the evaluation of the outcome. I have seen at least three and maybe even more types of outcome evaluations and, again, it is not clear to me how we compare those across studies, such as the percent less than 400 copies, the change in CD4 count, the change in log RNA, the time-weighted or unweighted averages.

Underlying all that is my next comment, which I will make brief, and that is the issue of missing **data.** I Eeel that the term intention-to-treat in this presentation is a lot different than what I am used to calling intention-to-treat. Although you are correct in trying to evaluate all randomized patients in an intention-to-treat analysis, if the outcome is at 24 weeks you don't **have** the data on all the patients at 24 weeks. I have been involved in other studies where this is also a problem. Fungal infection studies traditionally, for some **reason,** can't get the evaluations at the evaluation point. I think it is very critical in a study where we are using a surrogate endpoint to know what the outcomes were at the defined point in time, assuming those patients are alive and if they **are** not alive you can make an appropriate adjustment there, but if they are alive, even if they are not on drug. I will save the

rest for later.

DR. TOOLE: First of all, with regard to the comparison in study 408 for the percentage of patients that were less than 400, it is important to keep in mind that this patient population came in with a mean baseline of 30,000. What you are looking at there is adding adefovir on top of a background regimen. So you wouldn't expect to get many patients that go below 400 copies/ml in that type of study. Whereas, in study 417 they were started on an entirely new regimen.

DR. VERTER: If I could just comment on that, that is one of my points on how to treat the two studies. I recognize there was a difference and I am having a little trouble in using 408 to evaluate 417.

[Slide]

DR. TOOLE: The intent-to-treat analysis in study 417 was such that any missing observations were considered failure and because, as I showed earlier, there were more patients discontinuing at the higher dose group, that led us to look at an analysis where we use the last observation carried forward.

When we did that, there were 6 patients at the higher dose group who were now considered as less than 400 copies/mL at week 20, and there was 1 additional patient at the 60 mg dose who was now considered as less than 400

copies/mL at week 20.

So, that was our way of handling the missing data in that population. In doing that, the lower boundary of the 95 percent confidence interval is still minus 0.73 and within the minus 12 percent that we set for equivalence.

DR. VERTER: Can I follow-up on that? I guess that does highlight one my possible concerns. I did see that data and I appreciate your showing it again.

The problem I have -- and I would have to go back to the survival curves -- is if 20 percent, 30 percent of the patients have not completed the 24 weeks the analysis could infer equivalence or mask equivalence, or even mask harm, depending on what happened to those 20 or 30 percent. I appreciate the way you have done the analysis, and I think traditional clinical trial analyses by various authors suggest that is a good way to do it. But oftentimes I think there is a fewer percentage missing the principal outcome, and I still have some concerns about that.

DR. TOOLE: And it is hard to give a percentage less than 400 for any particular drug in a combination regimen. However, in nucleoside-experienced patients adefovir had demonstrated activity in study 408. So, we assume that it is making a contribution in regards to 'changes from baseline viral load.

DR. VERTER: One quick one, could you just tell

the committee, of all the ones that didn't make it, don't have the week 25 evaluation, how many had died by week 24 in each group?

DR. TOOLE: There were no deaths in the study.

DR. HAMMER: Thank you. Dr. Kopp?

DR. KOPP: Thank you. As a nephrologist, I have a number of concerns about nephrotoxicity but I think the central one has to do with the issue of reversibility, and I also have concerns about missing data.

First, I would like to ask in study 408, we have been told that 32 patients, that is 8 percent, at the time of last follow-up still had serum creatinines of 0.5 or greater. Also, the median follow-up in those patients I believe was 6 weeks, which was shorter than in the other groups. Do we have any further data on those 32 patients?

DR. TOOLE: I am sorry, could you repeat the question?

DR. KOPP: In study 408, the 32 patients, representing 8 percent of the total, at the time of last follow-up had a median time of 6 weeks of follow-up and had a creatinine elevation of at least 0.5. Do we have any further follow-up than what was presented?

DR. TOOLE: That was up to our safety update submission. That was part of the NDA. There is no additional follow-up in any of those patients.

DR. KOPP: Is there the opportunity to contact these patients again in some fashion?

DR. TOOLE: No, we have made significant efforts in trying to get these patients back. I think another thing that might be instructive is to look at slide 812.

[Slide]

We have presented two analyses. One was looking at the Kaplan-Meier analysis which would account for patients who were dropping out for being followed to resolution. Then there were 19 percent of patients that at last follow-up had not achieved resolution. However, many of those patients were not followed, as you stated, beyond 6 weeks.

We did an analysis looking for those patients for whom we had greater than 48 weeks of follow-up, in this case looking for patients who had creatinine increases greater than 0.5 mg/dL, and in 168 patients there were 10 patients that had greater than 40 weeks of follow-up and remained unresolved, so approximately 6 percent of the patients that had the abnormality. So, this would be somewhere in between the estimate of 19 percent which remained unresolved with significant follow-up.

DR. KOPP: I guess a follow-up question on that having to do with study 417, I believe it was 30 percent of patients on the lower dose of adefovir, 60 mg, who also

experienced a creatinine elevation of 0.5 or greater. What about resolution in those patients? I don't think data was presented there.

DR. TOOLE: There were 18 patients in study 417 that developed a creatinine abnormality of 0.5 or greater. At the time of last follow-up 12 had resolved.

[Slide]

Shown here are the data for those 6 patients who at last follow-up had not resolved. So, the interval of follow-up ranges from none to 42 weeks. Their last values range from 1.1 to 1.4 mg/dL. Looking at their baseline, nost of the patients are about 0.5 mg/dL fm baseline, so right at the cut-off for resolution.

DR. KOPP: Thank you.

DR. RAMMER: Dr. Kimmel?

DR. KIMMEL: I am also a nephrologist, and I vanted to pick up on what Dr. Feinberg was questioning. For ne to evaluate change of creatinine of 0.5 mg/dL, I need to :now what the baseline was and I was very interested in :inally seeing some baseline creatinine data on the slide :hat was just shown. In all the slides where you have the virologic data, you never have baseline creatinines. So, I vould like to know what was the baseline creatinine in study :08, 417 and in the expanded access group because that will ielp us evaluate how severe the magnitude of the disorder

is.

DR. TOOLE: The mean baseline creatinine in all of our studies has been 0.9 mg/dL.

DR. KIMMEL: So, you are using about a 30 percent loss of renal function.

DR. TOOLE: That is correct, however -- can I get slide 842?

[Slide]

Again, it is important to put that in context to look at the placebo arm of study 408 and look at their variability from baseline. When doing at -- and, again, this is the population at baseline of 0.9 -- 41 percent of patients in the placebo arm will have a 0.2 increase in sreatinine during the 24 weeks; 13 percent will have a 0.3 mg/dL increase; and 4.4 and 1.4. That is why we chose the 0.5 as being a more definitive marker of the development of nephrotoxicity.

DR. KIMMEL: Thank you. The second question I had is that as a nephrologist I am concerned about acute renal Eailure because it increases the mortality risk. I am concerned about hypophosphatemia because it increases the risk of death from sepsis. So, I would like to know in study 408 and the expanded access group -- I realize there was a very small number of deaths, but have you looked at the mortality risk conveyed by either hypophosphatemia,

using your definition, an increase in creatinine of 0.5 mg/dL or the combination?

[Slide]

DR. JAFFE: In terms of hypophosphatemia, other than the two patients on 120 mg who had renal failure, one with IV radiocontrast and the other setting I mentioned earlier from 039 who actually did not have hypophosphatemia but hyperphosphatemia, there is no apparent increase in mortality associated with hypophosphatemia.

[Slide]

In terms of deaths on the clinical studies, this is from the controlled clinical trials and there have been 6 deaths on the Gilead-sponsored clinical trials. Three expired 6 months to 2 years post the discontinuation of study drug, all from malignancies, and 3 others died while on adefovir, 1 for suicide and 2 multi-organ failures with numerous risk factors. One of the patients that I mentioned earlier that had the IV radiocontrast induced toxicity. So, there is no evidence per se in patients who do not have evidence of acute renal failure that there is increased potential for mortality.

DR. KIMMEL: But if you do a Kaplan-Meier on patients who had an increase in creatinine versus those who didn't -- I am not talking about needing dialysis -- or if you do a Cox regression on those patients, have you done

that?

DR. JAFFE: Well, there were only 6 patients --

DR. KIMMEL: I understand --

DR. JAFFE: -- in over 1000 patients, and I believe of these 6 only 2 had evidence of renal toxicity. So, I think it would be very difficult to show that there was, in fact, an impact of creatinine elevation.

DR. KIMMEL: I realize there was a small number of events. The last question I wanted to ask is I thought the data on the distribution of low bicarbonate levels and low phosphate levels was a little bit confusing because I couldn't really tease out how many of those patients were on phosphate supplements and how many were on bicarbonate supplements. It is very different to have a phosphorus of 2 if you are taking 60 nutrophos a day or a bicarbonate of 16 if you are taking 16 tablets a day. So, can you comment on the burden of therapy in those patients, the proportion of patients who were receiving supplementation?

DR. JAFFE: In the 408 study, since toxicity was unexpected, we were not planning prospectively to have phosphate administration so there is a very small number, I believe about a dozen patients who got phosphate supplements. In terms of bicarbonate supplementations, it is even smaller than that. I believe it is 6 patients or so.

DR. KIMMEL: And, that includes the data that we have seen on resolution figures?

DR. JAFFE: That is correct.

DR. KIMMEL: Thank you very much.

DR. HAMMER: Mr. Schouten?

MR. SCHOUTEN: I have one quick question for the FDA and then a little more detailed question for Gilead. In Dr. Jolson's review that was prepared, on the bottom of page 4 it said there was no difference in HIV RNA values at week 24 in Gilead trial 408, but Gilead has shown us data that is different than that for the 24-week HIV RNA data.

The other question is, I still would like to come back to this question about almost comparing apples and oranges by comparing 408 and 417. To get some sense of how comparable these patient population were, and they don't sound all that comparable, can you tell us how many people were PI naive in 408, and do you have any resistance data in 417, like we saw the virology subset in 408, to get a sense of how treatment experienced the 417 patients were who were PI naive coming into that trial to make some sense of comparing these two very different patient populations?

DR. HAMMER: Dr. Jolson, did you want to respond or clarify that first point?

DR. JOLSON: Yes, I wonder if you could just clarify your question, the first question that was addressed

to us?

MR. SCHOUTEN: In your review on 408, it was said there was no statistically significant difference with respect to proportion of patients with HIV RNAs less than 400 at 24 weeks, but we saw different data presented here this morning.

DR. JOLSON: That is correct. I think what you are referring to is that we did say there was a statistically significant difference for the DAVG at 24 weeks but there were no differences for the proportion less than 400.

DR. HAMMER: Is that a point of controversy or consent? The proportion below 400 copies at 24 weeks.

DR. JAFFE: In study 408? That is true according to the PCR technique. According to the bDNA technique, which was used for screening patients into study and was actually the assay that was to be used prospectively, there was about 19 percent of patients at 24 weeks who were below the cut-off of that Chiron assay and about 4 percent on placebo, and that was statistically significant I believe at 0.002.

DR. RAMMER: Is that the version 2 assay?

DR. JAFFE: Yes, it is.

DR. RAMMER: Thank you.

[Slide]

DR. JAFFE: So, there was a bunch of questions, but getting to the first one in terms of protease inhibitor therapy, this will show the distribution of patients at baseline on protease inhibitors, and one must be mindful that this study began in 1996, shortly after indinavir and ritonavir were approved. So, there were changes in the background therapies for patients enrolling on this study, whether they were there at the beginning of the study or at the end. So, there was more protease inhibitor use in patients who had enrolled late in the study. About 40 percent, 39 percent and 38 percent of the patients were on protease inhibitors at the time of enrollment.

I think Dr. Toole mentioned this earlier, we looked at the presence or absence of PI within a regimen at baseline, and compared to placebo the differences were statistically significant. If you were on a PI-containing regimen and you had adefovir added to your regimen, the mean change at week 24 was 0.33 compared to essentially no change on placebo, and that had a p-value of 0.016. If you were not on a PI at baseline and added adefovir or placebo, the mean change at week 24 was minus 0.43 compared to essentially no change in placebo patients, and that had a highly statistically significant p-value of about 0.001.

Your question then led into how does this compare with the 417 patients. I think the first thing to do is

refresh memory of the baseline genotypes from study 408.

[Slide]

This will show you in that particular study that 43 percent of patients had high-level AZT and 3TC resistance at baseline. An additional 15 percent had high-level AZT resistance in the absence of the 184. So, fully 58 percent had high-level AZT resistance at baseline. Only 8 percent of patients had no evidence of an RT mutation directed against AZT or 3TC.

[Slide]

The point of this slide is to show you what the background genotypes were in patients on 417. I think one important point is to note that these are less treatment experienced patients so one would fully expect, since the level of high-level AZT resistance at baseline is only 9 percent, that the group at large would certainly have -- we would have high expectations that they would respond to adefovir therapy, and consistent with the notion that they were less treatment experienced, 43 percent of the patients had no AZT or 3TC mutations.

MR. SCHOUTEN: I guess that answered my question and points out that the 364 nelfinavir comparison arm isn't a very fair comparison because that is a very, very different patient population.

DR. HAMMER: Dr. Verter?

DR. VERTER: I would just like to follow-up on your comment. I think what you said is correct and it also highlights the confusion I was having on my comment earlier. In the FDA analysis that was presented, you are, indeed, correct. The percent less than 400 was not significant. However, in the analysis presented by the company today, they used DAVG, which was somewhat of a different outcome, and that highlights exactly the point I was making earlier. There are many different ways of cutting this data and we need to understand which ones, how well they correlated, and what the implications are for each of them.

DR. HAMMER: Dr. Feinberg?

DR. FEINBERG: I wanted to follow up, Jeff, on your comment and the slides we just saw about genotype at baseline because in the company's presentation of the 408 virology substudy it was puzzling to me that adefovir had no statistically significant different impact on mean change in viral load from placebo in patients that had no NRTI mutations at baseline, and in patients who had low-level AZT resistance at baseline. I am trying to make that story fit together. If I look at the slide set -- I don't have the numbers.

[Slide]

Yes, that is the one. You know, in light of what you just showed in terms of the question about baseline

genotypes, it is disturbing to me that in the patients who are genotypically wild type there is no statistically 'significant impact of adefovir versus placebo.

DR. BISCHOFBERGER: As you may recall, the largest group of people, 71, belong to this group, number 6, and really the other groups are so small in patient numbers that that doesn't make a statistically meaningful comparison possible. You have to remember that these 11 patients -- about half of them are on adefovir and half of them are on placebo, and so you are really comparing 6 on one to 5 on the other, and that makes a statistically significant p-value not possible. That is the only reason.

DR. HAMMER: Thank you. I have a few questions also but in the interest of quality of life I am going to suggest that we break for lunch. We will come back and have a few more minutes for questions. We will return in one hour, at 2:10. Thank you.

[Whereupon, at 1:10 p.m., the proceedings were recessed, to resume at 2:10 p.m.1

AFTERNOON PROCEEDINGS

DR. HAMMER: Before we start the next session, Dr. Jolson has a point of clarification she would like to make.

DR. JOLSON: Dr. Hammer, I just wanted to clarify some of the earlier discussion that we had about pediatric use and the pediatric formulation, just so that the committee can take this into account as they consider the data.

I mentioned this to Dr. Yogev at lunch so even if he is not sitting there, he has heard what the issue is. The data that was presented was pharmacokinetic and safety data in pediatrics. Then there was some discussion about whether or not there was enough data to support dosing in very young children. At that time, I made a comment to point out that the pediatric formulation, which is being considered under a different NDA, is not the subject of today's discussion because, in fact, it was only recently submitted as a different formulation.

However, in the committee's deliberation today, remembering that we are considering a solid formulation of adefovir, they can consider what ages it is appropriate for including young children who are able to swallow a tablet formulation and, therefore, can take into account and consider the adequacy of both the safety and pharmacokinetic data to support use in children who can swallow a tablet

formulation. I didn't mean to imply that we were only considering use in adults. I was speaking more to formulation, and I just wanted to clarify that so that the committee can take that into consideration.

DR. HAMMER: Thank you. Do any of the committee members have a question about that? If not, we are going to take, hopefully, no more than 30 minutes for additional points of clarification and questions from the committee to the sponsor or the agency.

I didn't get a chance in the round to ask any questions and I am going to just make a few targeted points and ask for rather rapid responses from the sponsor, if possible, that hopefully will help us in our deliberations this afternoon.

The first question is about CD4 responses. We saw the CD4 results for study 408 and I think one other study. I think as part of a marker of response, it would be help for the committee to get perhaps a better overview picture of what CD4 responses are like with adefovir at the 60 mg dose, the dose we are being asked to consider today. So, are there additional data beyond the 408 study that the sponsor would like to quickly present?

[Slide]

DR. TOOLE: Shown here are the mean change from baseline with 95 percent confidence intervals from study 417

comparing the 2 dose levels from baseline out to week 20. As shown here, they are very similar. At week 20 there is an 86 cell increase at the 60 mg dose compared to a 76 cell increase at the 120 mg dose.

DR. RAMMER: Thank you, but that again raises the issue of the background therapy versus teasing out what adefovir is doing. So, are there any data that help us tease that out? For example, it may be in the packet, but in the 420 l-month monotherapy study?

DR. TOOLE: In the 420 study we looked at DAVG. For the active group it was plus 5 cells and for the placebo it was minus 40 cells but that did not reach significance.

DR. HAMMER: Thank you. One other quick question and, again, this relates to trying to tease out activity of adefovir when used in other combinations, would you like to comment on study 411 in the 4-drug arm versus the 3-drug control arm? Specifically when adefovir is added to indinavir, ZDV and 3TC there seemed to be no difference compared to indinavir, ZDV and 3TC alone. Is that impression correct, and would you please comment on that?

DR. TOOLE: That is correct.

[Slide]

That is true. Looking at the quad arm with the addition of adefovir to the control arm showed no additional benefit.

DR. HAMMER: And how do you interpret that?

DR. TOOLE: However, if one compares these two arms, you could also interpret that as saying that the addition of AZT to this arm also provided no significant additional benefit, or the addition of 3TC to this arm also provided no additional benefit.

DR. HAMMER: Yes, Dr. Yogev?

DR. YOGEV: Just in continuation to that, we just completed a study in the ACTG using a protease inhibitor with one NRTI versus two NRTIs and at week 24 we didn't find any difference while a difference that is showing up at 36 to 48 weeks. So I think part of the way to look at this drug -- maybe the time is too short to see if this drug is adding to what is there.

DR. HAMMER: Thank you. A virologic question, one issue that comes up in selection of resistance is that adefovir may not be selecting for mutations identified in the in vitro studies, but there is a continued evolution of nucleoside mutations, both in adefovir and control arms. Is there any evidence for increase or decrease, or is it similar as far as other nucleoside analog mutations? I ask this question because of the increasing amount of data that certain nucleosides can engender resistance not to themselves but to typical mutational patterns to other nucleosides.

DR. BISCHOFBERGER: We have seen in study 408 that the resistance mutations that come up in the adefovir-treated arm are mostly 67 and 70 and those, either alone or together, do not impart any reduced sensitivity to adefovir. That is why we call them AZT-associated mutations.

DR. HAMMER: And those are in arms that also do not contain AZT?

DR. BISCHOFBERGER: Some of those arms do and some of the arms contain D4T. So, there is a background of nucleosides and it is not readily apparent where those mutations come from. The best example is probably in 417 in the double protease arm. At the 60 mg dose we had one 167 mutation come up, and that has to be due to adefovir. That is one of the few arms where we had adefovir as the only nucleoside.

DR. HAMMER: Then I would like to ask the sponsor if you would like to comment on the FDA analysis of study 417, specifically regimen 3 and the saquinavir arm that seemed to under-perform in the presence of adefovir at 120 mg being somewhat of an outlier in response, and whether there is an interpretation to that. Is that a fluke or is that more likely to be something real, again raising the specter of a drug interaction? We heard from the FDA presentation that at least by a statistical test the probability was that that was not a fluke, but what is the

sponsor's response to that? I think it is important to hear your views.

[Slide]

DR. JAFFE: First, we will start by just looking once again at a slide you have already seen. This is to better understand the plausibility of an interaction between the 120 mg dose and saquinavir. I might also point out with regard to pharmacokinetics, if you look at exposure for patients receiving 60 mg and at patients receiving 120 mg, because of inter-patient variability, there is actually overlap.

Now, looking specifically at the idea that there may be a dose-specific interaction between 120 mg and saquinavir, we see no evidence to that effect. When we look at the other saquinavir-containing arm, nelfinavir plus saquinavir 60 mg, the intent-to-treat is 42 percent and 120 mg it is 44 percent.

Within protocol defined methods, we have tried to deduce or understand the homogeneity of response and whether or not this is a chance outcome, and I will ask Jim Esinhart from Pharma Research, the contract research organization involved with the performance of this study, to review those data.

DR. ESINHART: Dr. Soon presented the results of the logistic model. We defined, as part of the original

planning of the analysis, Braeslow-Day test and I am going to try to present this without a slide.

The resulting p-value from the Braeslow-Day test, which is analogous to the logistic regression, was 0.449. So, it is basically equivalent to a flip of a coin. We believe this p-value is large enough to exclude a clinically meaningful interaction.

In addition, this test was repeated at week 12 and the resulting p-value is 0.82, which supports the conclusions that these data are consistent with no interactions.

DR. HAMMER: And lack of interaction you are defining here as?

DR. ESINHART: The lack of interaction?

DR. HAMMER: There are at least two potential interactions here, dose and response, saquinavir-adefovir interaction. Which interaction are you excluding by this analysis?

DR. ESINHART: This was an overall test looking at overall interaction across the three groups, which is the protease-containing groups as well as the other dose levels.

DR. HAMMER: Dr. Verter?

DR. VERTER: I would just be curious, in looking at the tables, at the potential for looking at one or more of the interactions, there are only 35 or so patients in

each cell, and there are what appear to be some observable numeric differences, let's say because of the small numbers, and they don't go in the same directions across the groups. So, I am wondering if you did either any simulations or any other studies to detect -- you know, what ability did you have to detect an interaction, at what level?

DR. ESINHART: We did not do any further analyses.

DR. HAMMER: Thank you. I have one last question, and it relates to the ongoing studies for traditional approval because part of our charge today is to think about those studies in relation to our decision-making and the advice that we are asked to give. So, I would ask about the status of the two studies for durability that are planned, the target and where the enrollment stands, and when it started. I would also ask, as a corollary question, in the intensification study using adefovir, which has a high incidence even at 60 mg of nephrotoxicity at the 6-month or more mark, about the probability that patients will stay on that regimen through the 48-week time point. So, I think it is really where those studies stand for enrollment; when the target enrollment will be finished; and the issue of feasibility of actually getting the answer that you desire.

DR. JAFFE: With regard to study 415, that is a study that began, and was actually finalized with FDA input, in May of this year. We began enrollment at the end of May.

The target sample size is 390 patients, which will be enrolled at approximately 60 study sites around the world, with about half of the study site ex-U.S. We have currently enrolled approximately 100 patients on that study.

Study 458 -- we have only recently finalized that protocol with some input with FDA, and that protocol, which is being performed at a similar number of sites, about 50 with two-thirds of those sites ex-U.S., has just begun enrolling and randomized its first patient last week.

Now getting back to your question about the feasibility of looking at 60 mg long-term in study 415, when we have conducted placebo-controlled trials where patients do not have knowledge as to whether they are on active or placebo as opposed to dose-blinded studies, we have not had difficulty in keeping patients on drug for a long period of time. In particular, I would once again point to 039 where 38 percent of patients came off after about a year on active versus 32 percent on placebo.

DR. HAMMER: Thank you. I will now open this up for any last questions from the committee members on a random basis. Dr. Bertino?

DR. BERTINO: Yes, a kinetics question and a patient management question. It was disappointing not to see any data on sex or ethnic differences. I think it said not enough to draw conclusions. Given that one of the

nephrotoxicity risk factors that appeared to be protective was non-Caucasian, are you planning on doing any **male/female** studies and looking at ethnic differences pharmacokinetically?

DR. CUNDY: Yes.

[Slide]

We have actually looked at the effect of gender in our larger studies in the healthy, normal volunteers, and this was in 81 patients, 46 females **and** 35 males. All of these subjects were studied with a single dose of adefovir dipivoxil at 60 mg, and we used the FDA-recommended comparison, the l-sided T-test, and under these conditions the PK of adefovir dipivoxil was equivalent in males and females.

I could actually address the second question, which I believe was effect on race. If I could have slide 1114?

[Slide]

Most of our data from HIV-infected patients, more than 70 patients -- approximately 75 percent of that data was generated in African Americans. From our healthy volunteer data we have approximately 72 Caucasians, 3 native Americans, 3 Asians, 1 African American and 2 Hispanics and across this entire database there doesn't appear to be any effect of race on the pharmacokinetics of adefovir

dipivoxil.

DR. BERTINO: Thanks. Can I ask a question on a patient management issue?

DR. HAMMER: Sure.

DR. BERTINO: Looking at the flow-diagram in the briefing book, the question I have is what happens if a patient doesn't show up for his laboratory monitoring on a monthly basis? Are they not dispensed the drug?

DR. JAFFE: The language within the package insert, and it will certainly be emphasized within all of the educational materials associated with this product, is that you need to have monthly monitoring. In fact, we are going to take the step of having preprinted prescription pads that limit refills to only be provided if you have monthly laboratory monitoring.

DR. BERTINO: So, the answer is you don't get a refill if you don't have your monthly monitoring?

DR. JAFFE: That is the intention, yes.

DR. BERTINO: Okay. I see kind of a rock and a hard place issue here.

DR. HAMMER: Although I think it should be stated that if a physician doesn't use that prescription that is pre-prepared anything can be written. Dr. Feinberg?

DR. FEINBERG: I have a couple of questions here. One is a follow-up of what Joe Bertino just asked, but I

want to ask it not from a pharmacokinetic standpoint but from concerns about long-term toxicity. I actually thought it was striking that non-Caucasian race was protective. At best, less than 20 percent of all the people in the studies, including expanded access, appear to be African American in terms of race and ethnicity. Intuitively, since there is a greater risk of HIV nephropathy and possibly a higher incidence of just hypertension and other things that aren't good for your kidneys in that population, one of the crucial things that needs to be done for this drug is to have long-term clinical follow-up of people. I am curious as to why everybody was lumped together as non-Caucasian for that analysis. I would have certainly thought that looking at the African American patients separately would have been important, and it may be like some of the other questions I raised before, that the N here is too small to generate an answer. But when we met last summer, you know, a lot of our stated concerns were that we have adequate duration of follow-up of the nephrotoxicity both in general and then in specific populations.

DR. JAFFE: With regard to the multivariate analysis, non-Caucasians incorporated both Hispanics and African Americans. However, if you look at African Americans by themselves there is, according to the Cox regression model, a statistically significant reduction in

risk.

If we look at study 408 and focus in on African Americans, the incidence of renal toxicity, as defined by the creatinine elevation, was 23 percent compared to 41 percent in Caucasians.

DR. HAMMER: Dr. Hamilton?

DR. HAMILTON: Looking at that from the other side of the coin, is there any reason to think that this drug has any special benefits for those with HIV nephropathy?

DR. JAFFE: Well, it very well may based on accumulated knowledge on HIV nephropathy and active replication in sensitive cells. However, we do not have specific knowledge of how the drug may perform in that patient population, although we do have plans at some New York City sites to actually answer that question in a formal randomized study in the future.

DR. HAMMER: Mr. Schouten?

MR. SCHOUTEN: Yes, a quick comment on the no lab, no drug. You know, for my antiretrovirals I save a significant amount of money if I mail order for 90-day supplies. So, one-month limitations would cost me a significant amount of money in added co-pays.

Two other things, in following up on the resistance question I asked earlier, because I think your proposed indication is targeting people who have failed

reverse transcriptase inhibitors in the past and your data set in 408 was too small to address the wild type group but in 417 you have a much larger group of wild type. Have you looked at a subset analysis of response in the two dose arms based on background resistance in your 417 database?

DR. JAFFE: Yes, we have and consistent with the overall result of the study, there really is no difference between the two different dose groups with regard to background genotypic mutation at baseline.

DR. HAMMER: Dr. Lipsky?

DR. LIPSKY: I have a question for the agency. In the presentation there was a slide on study issues in 417, and the very first item was "not intended as a registrational trial," and then a group of agency concerns. Was that at the beginning when this study was proposed? Can you put that in some sort of context? Because when we left here a year ago, August, there was talk about an induction phase at 120, lowering the dose to 60. It was unclear where we were going. From the agency's perspective, what was the evolution of your concerns of 417 and what happened?

DR. STRUBLE: I think that study 417 was submitted like a Phase II trial where they were assessing 60 mg versus 120 mg. All along, the sponsor was evaluating the 120 mg for registration. One the toxicity in 408 became a concern, then that study which was never intended to serve as a

registrational trial gained much greater importance because there had been a dose reduction. So, that is what we were faced with, with a trial that had already started to enroll. The intention was never to be a registrational trial, and then subsequently the focus shifted for the 60 mg.

At the time of the closed session last year we had talked about other strategies -- you know, 120 mg for 16-week induction followed by a dose reduction to 60 mg, and after further consideration it was decided that the 60 mg up front would be studied all along.

DR. LIPSKY: And when were the concerns about powering the study, confounding issues of the multiple therapies -- 1 am a little confused. This was ongoing or did this -- I mean, you raised these issues and nothing happened, or what?

DR. STRUBLE: Well, we raised the issues that, now since the 60 mg was going to be the dose that they were choosing to market, we had issues with the 417 trial: the complex treatment regimens, the 20-week time point. We had given advice about how to increase the sample size and maybe pick other comparisons, and this is what we were left with at the end of the day.

DR. LIPSKY: I see, and was there ever consideration of having a placebo group?

DR. STRUBLE: No, not at the time.

DR. RAMMER: Dr. Yogev?

DR. YOGEV: Can the company explain to me, in study 408 versus 417, the percentage of patients in the 120 mg group who had onset of serum creatinine increase at week 28 is 20 percent versus 40 percent, and for the phosphatase it is almost zero versus close to 40 percent. Why is there a discrepancy?

DR. JAFFE: Sorry, your specific question is looking at the Kaplan-Meier plots?

DR. YOGEV: Correct.

DR. JAFFE: So, why there is a small increase in patients who had creatinine elevations in 417 earlier on than in study 408?

DR. YOGEV: If you take week 28, does that suggest the populations are so different? In one study you have 40 percent and in the other one you have almost zero for the phosphatase toxicity. Is that part of a different population and we need to pay attention when we predict when toxicity can come out?

DR. JAFFE: We do not have an explanation for that.

DR. KOPP: I noticed that in your proposed treatment guidelines or toxicity management guidelines that if patients have a creatinine elevation of 0.3 to 0.4 they be dose reduced from 60 to 30. I know earlier you said you

had 42 patients in 411 and 417 treated with that dose of 30. Can you comment about what happens to toxicity? My concern here is that if we know we have a patient with significant renal toxicity, what happens from continuing to give a nephrotoxin, albeit at a lower dose?

DR. JAFFE: The best data that deal with the issue of continuing drug exposure in the setting of toxicity actually come from study 408 where we have longer-term follow-up. In the patients who developed creatinine elevations, 70 percent had their resolution when they came off study drug. However, about 30 percent of the patients actually went down to 60 mg and had resolution of their creatinine toxicity, and a full about 5 percent of patients actually stayed on full dose, 120 mg, and had resolution. So, in terms of going from 60 to 30, we would expect that something similar would occur. However, we are being very, very cautious in terms of the management guidelines and we are recommending that patients came off the drug if they have a further increase. The patients that Dr. Toole showed with the mean change, were patients were continued on 30 mg for about 4 or 5 months and we expect to have more data in the not too distant future without continuous increase in creatinine.

DR. KIMMEL: I have another question about the dosing guidelines, which refers to stopping treatment and

then restarting treatment over what seems to me a variable period of time, depending on the resolution. Are you concerned about resistance in those patients?

DR. JAFFE: We have not seen anything to suggest that we would develop resistance. In those patients that we have dosed at very low doses for short periods of time we have not seen anything to suggest that resistance will develop. However, as part of the Phase IV program we certainly will be following patients closely to see if that, in fact, occurs.

DR. RAMMER: Dr. Mathews and then Dr. Feinberg and then Dr. El-Sadr.

DR. MATHEWS: In a number of your trials you monitored serum carnitine levels, and the proposed supplementation -- 1 didn't see anything calling for monitoring of carnitine levels. In your background you said using 500 mg of carnitine maintained the level in the normal range in the vast majority of patients but not all, and I know some patients have been supplemented with more than 500. so, what is the actual data on carnitine depletion and the adequacy of the 500 mg dose?

[Slide]

DR. JAFFE: What we have here are longitudinal data from study 417, the dose comparison study. You are looking at mean free carnitine concentrations in the serum.

At the 120 mg dose with supplementation of 500 mg of carnitine, you can see that there is a decrease to a nadir of about 75 percent, 80 percent which, by week 48, is now about 80 percent. For 60 mg, a similar pattern but by week 48 it is about 95 percent of baseline. We rarely see patients who have gone below the lower limit of normal with patients on 60 or even 120, and when that does happen we believe it is because of an effect on the renal tubular cells, not being able to reabsorb filtered carnitine.

In terms of what this means clinically, there are many examples of other drugs that are administered chronically, and perhaps the best studied one, although the mechanism may be somewhat different but, nonetheless, it leads to decreases in serum carnitine to about 40-50 percent of baseline levels, is the anti-epileptic drug valproic acid which is used chronically, and I believe it is the most widely prescribed anti-seizure medication in kids, and supplementation with carnitine is not used in that patient population because there is no evidence that there are any symptoms or clinical sequelae related to carnitine deficiency. That, in fact, is the case in our clinical studies as well. We have not seen anything to suggest that decreased levels of carnitine have any clinical sequelae.

DR. MATHEWS: This may be a different situation. For example, zidovudine myopathy has been associated with

carnitine depletion, and it is going to be used concomitantly with adefovir. So, I am not so comfortable without monitoring in some way carnitine depletion.

DR. JAFFE: Well, we understand your concern. This drug has been dosed in combination with AZT in, I am sure, thousands of patients without any evidence that there is an increased incidence of myopathy or neuropathy. Perhaps one of our consultants, Dr. Charles Stanely, could come up and comment on the significance of the types of levels of free serum carnitine that we are seeing.

Dr. Stanely, by way of introduction, is in the Department of Pediatric Endocrinology at the Children's Hospital of Philadelphia, and I think it is fair to say that Charlie has spent a good deal of his professional career looking at primary and secondary deficiency states for carnitine.

DR. STANLEY: Maybe the simplest way to talk about the issue of carnitine depletion is the one clinical situation we know of where carnitine depletion causes clinical symptoms is in the genetic defect of the carnitine transporter. Those children have muscle carnitine levels and serum carnitine levels that are reduced about one or two percent of normal, and treatment with carnitine that gets their muscle levels back to five percent of normal eliminates their clinical symptoms. So, a small reduction

in carnitine levels that have been seen with this drug are not very significant.

In terms of the myopathy with AZT, that seems to be a mitochondrial DNA depletion problem, and **a secondary** carnitine deficiency associated with blocks in mitochondrial metabolism is a quite frequent occurrence. But carnitine deficiency in that situation is a consequence of a metabolic block rather than a cause.

DR. HAMMER: Dr. Feinberg?

DR. FEINBERG: I have I guess an editorial comment and then **a** question. My editorial comment is that with regard to the resistance profile for this drug, I guess all I want to say is **that** it seems to me a bit sanguine to say that resistance development isn't very much anticipated. The likelihood that it may require multiple mutations to create solid resistance to this drug is quite real. The K70E only gives you 3- to 9-fold reduced susceptibility. I remember that it wasn't until the second year of AZT monotherapy that we saw the clinical impact of resistance development, and not very many people have taken this drug for **an** extended period of time. So, I am not so sure we are there yet.

My question to the sponsor is there are three trials in experienced patients, one that has statistically significant favorable outcome and two that do not. The two

that do not were the federally funded trials, the ACTG and CPCRA studies. In our briefing documents, apparently the FDA had only the executive summaries for those, and so I would like to understand why the agency didn't have access to those data sets, if someone could explain that, please?

DR. MURRAY: I think that the 359 results were still quite preliminary at the time when the NDA was submitted. I don't know if I have an answer for the CPCRA 039 study. Gilead did do some of their own analyses and so, you know, I guess it was probably a little bit more than just an executive summary. We did have a little bit less for 359. You know, by the regulations though if there are studies that are out there that are relevant or, you know, could even cast doubt or speak to efficacy or safety, they need to at least be mentioned with the caveat that we are not able to, you know, review all data. Sometimes, you know, these studies get finished at kind of inopportune times, and I think that that was at least part of the problem.

DR. HAMMER: But there were some FDA analyses of 039 for looking at some of the baseline covariates for RNA and other things --

DR. MURRAY: Exactly, yes.

DR. HAMMER: -- and those were presented this morning. So, you did have access to some data sets to allow

you to make those analyses.

DR. MURRAY: Right, right.

DR. HAMMER: Dr. El-Sadr, do you have a question?

DR. EL-SADR: Actually, I have a couple of questions. I guess when you were doing 408, at that point we really didn't know about the nephrotoxicity yet and the patients were not getting the monthly monitoring. In that study, in 408, about 40 percent of the patients, by week 48, developed the serum creatinine increase. Now, in contradistinction, I think in 417, where you were doing the monthly monitoring for the serum creatinine, exactly the same percentage of patients developed the elevations in creatinine by week 48 also.

So, are you saying that if we monitor these patients carefully every month that we are going to somehow prevent this from happening? Because it seems to me that it didn't make a difference in the percentage of people who actually had the exact same abnormality.

DR. JAFFE: One, I think you decrease the incidence when you go from 120 mg to 60 mg. So that is one important point. But in terms of the management strategies and the following of patients with monthly laboratory monitoring, the important point there is that we limit the potential of increasing the renal toxicity so that patients would either dose reduce or come off drug.

I think an analysis that the FDA has done, one that we have both done and I think agree with the results, is that in study 408 70 percent of patients would have had an antecedent smaller increase in their creatinine that would have led to a dose reduction ahead of a potential doubling of their creatinine. If we had known about the utility of the monthly monitoring, many patients would have had less of an increase in their creatinine. And, we expect that the same would apply at least as much in the 60 mg dose. That is why when you look at the graded toxicity in 417 you see that there are no patients who have gone above creatinine 2.0 mg/dL or grade 3 toxicity on the 60 mg arm.

DR. EL-SADR: You had no difference in the proportion of people. Another question I have, and maybe I am confused about this, this morning one of the very early slides that Dr. Jolson showed was about the requirements for accelerated approval. They indicated two studies with at least 24 weeks of data. So, which studies are we considering? One is 408 and the other one is for accelerated approval? Because the other study, 417, only has 20-week follow-up, not 24. Right?

DR. JAFFE: I mean, we would have to ask the FDA to comment as well. I think they showed a draft guidance for industry slide. However, at the time the program began, and we made reference to this earlier in the day, at our end

of Phase II meeting, in April of 1996, we discussed one study, study 408. As correctly pointed out by Dr. Struble, at that time we didn't even discuss studies 411 or 417. They were intended principally when they first began as studies that would help round out the safety database, and took on more importance as we became aware of the dose-limiting nephrotoxicity at 120 mg.

DR. EL-SADR: Which are the two major studies for accelerate approval that are being proposed?

DR. JAFFE: Well, I think we would have to say 408 and 417.

DR. HAMMER: Dr. Pomerantz, and this will be the last question before we move on.

DR. POMERANTZ: I agree.

[Laughter]

I forgot one from this morning though, sorry. I was interested in the things to come in the future and the "intensification" study that was labeled 415 in which ADV is going to be added to some regimen. Now, I would be interested to know, this is a single addition of ADV to intensify people who are failing therapy, who have gone to 400 but not 50, and do you really think a 0.3 as a single drug is going to be a good intensification step?

DR. JAFFE: It is intended for patients with viral load at baseline of between 50 and 400 copies, and the idea

is to add on 60 mg or placebo, and the primary endpoint is not driving patients below 50 copies but time to virologic failure. So, the hypothesis is that patients would stay below 400 for a longer period of time with the added benefit of adefovir therapy.

DR. POMERANTZ: So, you look at below 50 as a secondary endpoint?

DR. JAFFE: Yes, that is correct.

DR. POMERANTZ: Thanks.

DR. RAMMER: Thank you. Dr. Jolson?

DR. JOLSON: Maybe I could just get back to Dr. El-Sadr's comment about what are the two studies. There certainly are more than two studies in this application. Probably when we say two studies here, we would consider one of the two studies to initially support the safety and efficacy of 120 mg, and that would probably be the 408 study and the 411 study, even though 411 is in a population that they are not seeking an indication for. Then 417 would be looked at as trying to make the bridge between 120 mg and 60 mg. The exact length of the duration is probably more relevant to consider in terms of safety considerations for the drug than necessarily conforming exactly to what the guidance document says. That is a general recommendation. So, the duration should be really whatever duration you all have considered to be the minimum necessary to characterize

the safety and activity of the 60 mg dose. So, hopefully, that clarifies how we would look at the application.

The other studies that we talked about, the CPCRA study and the ACTG 359, would then be looked at additionally as studies that would have to be taken into account in the entire equation as you evaluate the package.

DR. EL-SADR: So, from you perspective, from the agency, you do not require two studies with 60 mg since that is the dose we are being asked to approve.

DR. JOLSON: No, if you will recall the slide that I showed this morning, what we would usually require is a bridging strategy and that would be whenever there is a significant change, in this case dose, or if there were a change in regimen or a substantial change in formulation such that the pharmacokinetics are different. Usually, once the initial safety and efficacy is established, we then require usually a single study to make that bridge such that you can basically say that there is a connection between what is known about the initial product and what is the known about the proposed product, the to be marketed product. In most cases, it is usually a single study. That is why that 417 study becomes really critical in your discussion in terms of whether or not that study makes an adequate link.

DR. RAMMER: Thank you. We need to move on now to

the open public hearing. There is a substantial number of people who have signed up in advance. There are a couple of preliminary comments. One, if you have not signed up in advance but wish to make a comment you will be permitted to at the end of the list of individuals who have signed up. Because of the numbers who have signed up, I would ask people to please try to limit your comments to three minutes in fairness to everyone else and so that we can move through the afternoon. Also, when you come to the microphone please identify yourself and the organization you represent. Please also disclose any financial interest in the product at hand today, and also any travel support to this meeting. If you have specifically no financial interest to report, please so state for the record.

The first individual who has signed up on our list is Dr. Sandra Burchett, from Harvard Medical School and Children's Hospital.

Open Public Hearing

DR. BURCHETT: Hi. I did have travel support to come today. I am at Children's Hospital in Boston, and there I am clinical director of **a** program that follows about 130 HIV-infected children. We have had opportunity, because most of the children who are infected have perinatal infection and are, therefore, infected for a long period of time and are long-time treated patients, to look at children

with advanced disease who have undergone multiple levels of therapy.

We have had 10 subjects enrolled to the expanded access protocol with adefovir, and of those, 7 children have received adefovir longer than 4 months in my clinic. They range in age between 9 and 15, and the duration of therapy is between 16 weeks and 40 weeks. Of those subjects, if they started out with greater than 200 CD4 cells, they had a substantial increase in their CD4 count. One example is rising from 800 to 1200, with a fall in viral load from 500,000 copies/ml by the Amplicor assay to less than 40 within 1 month. That child maintains his non-detectable viral load and is doing well on therapy.

There are two children in that group. There are five children in the other group that began with fewer than 200 CD4 cells, and in that regard all children had an increase in their CD4 count. Another example would be something like 75 to 300, with a fall in their viral load. Examples include 750,000 down to 200,000, or down to 5000.

These children also received at the same time additional agents that are included, as many as 8 drugs or at least 4 drugs were also given, and all children received at least 2 new agents in their combination.

The subjects in this group then have done well on adefovir combination therapy, except for one child who did

develop Fanconi renal syndrome at about 20 weeks on therapy. The children and the nurses in our clinic like this agent because it is once a day, because it is also available in liquid formulation that is also palatable. If you have tasted it, it doesn't taste so terrible. And, the kids are in school so that this is helpful for them, to be able to take something that is once a day and they can take at bedtime. Thank you.

DR. HAMMER: Thank you. The next speaker is Dr. James Jones.

DR. JONES: Good afternoon. My name is Dr. James Jones and I did have travel support to get here this afternoon. I am in private practice, mostly HIV medicine, The majority of my practice has been HIV for the past ten years. I am Board certified in internal medicine. I am associated attending in medicine at St. Luke's Roosevelt Hospital Center, in New York, assistant clinical professor of medicine at Columbia University College of Physicians and Surgeons.

To date, I have had 24 patients enrolled in the adefovir expanded access program. The majority of these patients were going on their third regimen and, besides being protease inhibitor experienced, were heavily nucleoside reverse transcriptase inhibitor experienced. out of these 24 patients, 16 remain on drug at this date, with a

range of 4-18 months on adefovir. Four patients have discontinued adefovir secondary to nephrotoxicity. The earliest incidence of nephrotoxicity occurred at 8 months. All of these 4 patients resolved their renal insufficiency with discontinuation of drug. One out of 24 patients discontinued secondary to non-compliance with his antiretroviral regimen, and 3 patients out of 24 expired secondary to complications of HIV, 2 cases of PML and 1 case of fulminant hepatic failure due to hepatitis B.

In these patients there were very few early adverse events, mostly mild and nausea which resolved without a change in therapy. While in the setting of a salvage regimen where numerous agents were changed in an attempt to improve the outcome it is impossible to judge the efficacy of one agent, I can say that in the 4 patients who stopped their adefovir due to nephrotoxicity, adefovir was the only agent that was stopped and there was a rebound in viral load in those patients.

My feeling is, with my experience with adefovir, that this agent offers a significant option for salvage therapy with convenient dosing and very few early side effects, and I feel that the nephrotoxicity observed with this agent can be easily managed with proper and timely monitoring. Thank you.

DR. HAMMER: Thank you very much. The next

speaker -- my apologies in advance if I mispronounce the name -- is Dr. Paul Cimoch.

DR. CIMOCH: Mr. Chairman, advisory members, as a matter of background, I did receive travel support to come to this meeting. I am Medical Director of the Center for Special Immunology where I do primary care and clinical research exclusively for patients with immune disorders. After University of Miami in the early '80s, I have managed and evaluated well over 1500 patients with this disease. I am also a clinical assistant professor of medicine at USC, and Board certified in internal medicine.

Like many HIV specialists, over the past two decades I have witnessed patients struggling from one small HIV scientific advance to another. In recent years though, through the use of HART cocktails, we have seen patients literally go from bed-bound to back to work. Yet, despite these advances too many patients continue to fail our currently antiretroviral treatments and many patients are exhausting the regimens.

In this context, I was delighted to be part of the adefovir expanded access program. Please note that all of my patients enrolled in this program are highly treatment experienced, on the average treated with at least five prior antiretroviral agents and usually on their third or fourth antiretroviral regimen. Sixty-two patients were enrolled