fully work up all those suspected of liver disease.

DR. ENGLUND: Dr. DeGruttola.

DR. DeGRUTTOLA: Yes, I want to agree with the need for longer-term clinical efficacy studies. I think this is a setting in which it's particularly hard to interpret the surrogate endpoints--both the virologic endpoints and some of the liver enzyme information.

I also think that it's important to make the best use of mutations at the start of treatment to try and identify patients who will have a non-durable response. Patients who got a 1-log drop but did not go below detection were considered as successes in this study, but I think finding out whether they have a durable effect, and also finding out whether it's possible to predict who will get a short-term but not durable effect, who will get a durable effect, and who won't get any effect--making the best use of the information at

baseline is also important.

And, similarly, in terms of predicting toxicities, I think it's important to try and classify both patients who will be at most risk, and also try to identify both the group of patients for whom one can predict that toxicities will be relatively modest or acceptable; and also patients in whom we just don't know, including--as has been mentioned--for women--so there are patients for whom we can say they will be at high risk, and patients for whom we might be able to say they're at low risk, and also patients for which the risk isn't well enough established.

DR. ENGLUND: Dr. Wood?

DR. WOOD: In addition to the comments that have already been echoed by my colleagues regarding the need to assess the durability of effect, as well as clinical outcomes, I think it's going to be very important that with the approval of this drug it's made clear to practicing clinicians that there really is--based on the data that was presented--no indication for tipranavir if an individual has

evidence of susceptibility to other licensed protease inhibitors, simply because development of tipranavir resistance mutations is then associated with cross-resistance to other PIs.

I also thing that, based on the data that we have regarding drug-drug interactions with other PIs, it appears, preliminarily, that tipranavir would really be the only protease inhibitor allowed in a regimen because of the presumed decrease in efficacy, based on diminished AUCs and C mins of amprenavir, saquinavir and lopinavir. Because right now, in terms of salvage approaches, many clinicians are using one or two PIs in addition to other nucleoside analogs.

The other thing that I think needs to be reinforced that, in terms of assessing the benefit, it really needs to be reinforced and made clear that tipranavir--in a heavily treatment-experienced population--really does requite another active drug; a drug with a high probability of activity.

I think the data was very strong and very consistent for T-20. I think the reason it is is

because that's generally the one drug that most heavily treatment-experienced people have not seen because of the formidable challenges associated with its administration.

I think that we also need to, in addition to focusing on the drug-drug interactions and looking at the anti-lipidemic agents because of the tipranavir-induced changes in cholesterol and triglycerides, I think another priority focus needs to be with anti-diabetic agents. Many patients who are heavily treatment-experienced also experience lipidistrophy. They have already evidence of insulin resistence, or frank and overt diabetes required in their co-management.

So identifying those drug interactions with tipranavir would also be something that I would consider a priority--in addition to looking at additional oral contraceptives in women. That has got to be just at the front gate. Because the is that one thing that's reinforced among all practitioners, particularly for their female patients, is the need for contraception. And it

will be very important to know about those drug interactions.

DR. ENGLUND: For the non-voting people, I would be happy to have you say something, but it's going to have to be pretty short. And I first get to add something.

And I'd say, in addition to oral contraceptives, certainly in the adolescent clinic we aren't trusting oral contraceptives at all--zero. And we need information on some of the other contraceptives--the patches and the implantable contraceptives. That's my opinion.

And next, Ms. Dee.

MS. DEE: Thanks.

You know, I think I don't have anything to add to what people said about what needs to be done. And I'm watching the indication shrink as--that 11/4 get qualified as we go around the room.

But I would like to know from the agency what authority do they have to say: "Okay, this is what you need to do to educate patients and

physicians--"--just about the drug interactions. And to the applicant: what do they plan to do to let people know that if you do certain things--I mean, this drug is going to be decreased, and that one's going to be increased. I mean, there are some pretty severe problems here with what we have, and what we know now.

DR. ENGLUND: I'd like Dr. Birnkrant to answer that, but first could I just have if there's any comments from the rest of you.

Dr. Fish?

DR. FISH: In terms of the clinical events that were discussed in terms of 24 weeks, I don't think--and the FDA can comment on this--that we would expect to see a difference within the 24 weeks.

So it is a casualty of an accelerated approval type of drug because of the situation of the highly treatment-experienced patients that are needing this drug.

In terms of the follow-up monitoring, the only other thing I would add is monitoring for

coronary artery disease risk, and cerebral vascular disease risk, given the lipid abnormalities that have been seen.

DR. ENGLUND: Dr. Kumar.

DR. KUMAR: I have a little bit different take on this whole thing than my colleagues around the table--especially the hepatologists. And I just want to come back and be able to publicly state that.

And I hear all the concerns that especially hepatologists raise and the clinicians around it.

But to me, as a clinician--and I went back and looked at these clinical trials and who were the people studied in these clinical trials?

85 percent of the patients that were in RESIST 1 and RESIST 2 had an AIDS-defining event; about half of them had at least received five different protease inhibitors. So this was an extremely treatment-experienced group of patients.

And in those patients--of course we worry about safety, whether it's liver, whether it's

lipids, whether it's rash. But I want to come back to say that the [XXX sounds like BAH] in which we look at these very heavily treatment-experienced patients is a lot different from a naive patient population. And all the concerns that we raised I think should not deter from the fact that at the present time this is one of the few agents that we have that are shown to be effective in such a highly treatment-experienced patients.

I would like to be able to say that, as a clinician: yes, we're concerned about toxicity. And to me, what I would like to--as I read through all the data is to look at which is the patient population that's heavily treatment-experienced, that needs the drug, that we can safely give it to. And there a number of them, because even the patients that developed hepatitis, in many of them, it resolved despite continuing the drug.

So it's really to determine what Dr. DeGruttola, you said, is to look at the people that will best benefit from it, and can be safely monitored on that drug.

Regarding durability, that was raised by many of my colleagues around the table: no single agent, no matter how potent it is, is going to be

durable if there are no additional drugs associated with that. And so that burden cannot be put on tipranavir to say that it's not durable. It's to say what can we do to have other durable agents, and to have clinical trials; not that the issue is that they don't allow investigational agents to be added on. And that's what they end up doing sequential therapy.

It's, you know, what can we do to have other more potent drugs down the line to be added earlier on in clinical trials.

DR. ENGLUND: Thank you.

And Dr. Haubrich.

DR. HAUBRICH: Well, I certainly agree with all of the suggestions about trying to define the population and monitor for safety. I think my comments are most closely aligned with Dr. Kumar.

The one thing that struck me here is that when studies like this were designed, we were all

applauding them because they didn't require maintaining patients on a failing regimen in the control arm. That type of design is completely contradictory to being able to show a clinical benefit, because all of your control-arm people drop out of the study.

There is no way this study was designed to show a clinical benefit. And I'm actually a little bit concerned that if there's calls to do such a study it will detract from doing the many other things that people have reported here that are much more important.

I personally believe--and the agency changed the way that drugs are approved in 1995 not to require clinical endpoint in studies. So even though we certainly would like to see that drugs benefit patients and keep them alive longer, I think that the cost and--you know, just trying to get people to do a study like that would just be infeasible, because you'd have to keep people on a control arm, which no one wants to do.

So, although I echo all the things that

need to be done to determine safety and drug interactions, I think that it isn't feasible in this day and age to design a study to look at clinical endpoints--and hope that people would stay away from that recommendation.

DR. ENGLUND: Dr. Birnkrant?

DR. BIRNKRANT: In follow-up to the question related to educational materials: we believe it's in everyone's interest--the agency, the company, the treating physicians and the patient's--that there be adequate educational materials. And I'm sure Boehringer Ingelheim could prepare a very thorough and detailed program.

But what we never seem to get is whether or not these educational programs actually work. So we have companies preparing various slides and other types of materials for practitioners, and patients as well. But we never get that next step, which is a testing--an actual formal testing--of the materials in a large group of those actually using the drug, with the condition, etcetera, to see if it really pays off.

My hope is that educational materials will be developed that will be adequate, and that physicians who, in general, do not treat this type

of patient population will refer to those with a lot more experience.

But again, as you mentioned--or someone mentioned--that's not something we regulate--for the most part.

DR. ENGLUND: I would like to briefly try to summarize, before we move on to the next question. And I think I'd like to say that we, as a Committee, feel that the need for this drug in our patient population is high. The potential benefits are high. The risks are certainly present, and that we as a group have concerns. Some of these concerns can be addressed in the company with long-term studies, and these studies--as pointed out by Dr. Haubrich--should involved long-term follow-up.

We want to know durability of these drugs. We want to know long-term interactions. We want to know side effects that are clinical. I don't

believe we need clinical endpoints, but we need clinical incidence rates; what is coronary artery disease, what is going on with diabetes, what is going on--and how are the doctors in your trial, which is widespread throughout the world--how are you helping them manage their patients. We could translate some of that into our clinics--although you certainly have more pull, during the clinical phase of testing.

We have questions, as a group, concerning management of toxicity, management by specialists, management with drug-drug interactions--which are clearly not all answered, and that will be a problem from day one of use of this drug in the clinic.

We have a concern of when to use additional drugs. We have a concern of which resistant data should we be using, and it needs to be defined clearly for even physicians in experienced clinics.

I think most important of all--this has bene repeatedly brought out by many of the

non-physician and physician members on this panel--and that is the lack of women in the studies. And to hear that the ongoing studies are not even preferentially enrolling women in studies, or setting up clinic studies where women are targeted, to me is still not appropriate. I think we could be doing studies out of OB/GYN clinics to try and get increased women, particularly when you have this background noise signal which has pointed out, related to oral contraceptives. And I think this could be brought, and it needs to be importantly raised up.

We have studies that have been requested--and these some in my notes. In terms of regarding liver, we need much more information on liver and hepatic function, and long-term hepatic function; output on cholesterol and hypertriglyceridemia; on predictions of toxicity from baseline; of rash incidence; and, again, of women.

With that--Dr. Birnkrant?

DR. BIRNKRANT: Two more things: one is Dr.

Murray would like to make a comment. And the second thing is I'd like maybe five minutes--10 minutes, max--discussion on the indication.

First we'll hear from Dr. Murray.

DR. MURRAY: Just as somebody who's been with this division for 13 years, and has sat through every Advisory meeting since ddC approval--

[Laughter.]

--[laughs]--I felt like I wanted to say something about clinical endpoint studies, because in addition to the drug-specific advisory committee meetings, we've had several topic-specific meetings, including the validation of HIV RNA, which I helped to participate in to a large part in 1997, and then there was a salvage committee meeting in 2000. There have been many other salvage meeting nationally--one hosted by the Forum. Veronica Miller was instrumental in that. But there's been several others.

And so I just have a comment on clinical endpoint studies for registration.

I think that, over the years, both

investigators and participants have decided that--or have told us, many times, at many meetings--that those trials are not the type of trials that they think that can be enrolled and that participants now want to participate in for the salvage population.

If you will remember, one of the last clinical endpoint trials, for ritonavir, in an advanced population, with a median CD4 cell count of 20, participants were made to stay on for 16, 24 weeks--whatever time period--until they actually had an opportunistic infection. They could not switch over. If they were on the control, they could not switch over to the active drug. And in a salvage population, many instances, you're going to have a suboptimal control because you won't necessarily have a lot of new drugs to combine it with.

Participants and investigators, at the time, thought it was not palatable for participants; it was unethical; and they no longer wanted to wait until somebody has CMV,

pneumocystis, MAC, on a comparator arm before they were allowed to switch.

So, in a salvage population, if you want clinical endpoint studies, you have to be willing to wait for a patient to physically fail and have an opportunistic infection.

With the onset of viral load monitoring back in 1997, I thought that we had--and then the salvage meetings back in 2000, and all the other numerous meetings--I thought really that this issue of clinical endpoints in the salvage population had been--for registrational purposes, not strategy trials. That might be different--had been laid to rest.

So, I mean, if it's still an open question, I would like everybody to really think hard about what it means for a salvage patient to participate in an HIV clinical endpoint study in 2005.

DR. ENGLUND: DR. DeGruttola.

DR. DeGRUTTOLA: Yes, I don't think there's any doubt about the difficulty any kind of a study

in a salvage population. And as Dr. Murray noted, you certainly can't do a salvage study which is requiring patients to stay on a therapy that they and their physicians have a high degree belief is ineffective and there's a better therapy available.

But I think there are some other factors that we need to take into consideration.

One is that when we're using surrogate endpoints, we're doing so because we have a belief that those surrogates will tell us, ultimately, whether the treatment effect on the surrogate is going to predict a clinical benefit.

And it's not at all--I think this is a case study of when it is particularly difficult to make that kind of an inference. Because we have a situation where there's a clear effect on the surrogate--the short-term viral load--in favor of efficacy; there are clear effects on surrogates and some clinical effects that are adverse. And what we're asked to do is to somehow come up with a model--whether an actual model or just an idea in our head--that allows us to combine all of this

information and compute some kind of risk-benefit that will tell us: yes, making this drug available is going to be to the benefit of the patient population; or no, we think it won't.

And I think just the amount of diversity of opinion on this panel here indicates that we can't really do that prediction at this point.

Now, on the other hand, no one is saying that we should be attempting to do studies that either can't enroll, or request patients to do something that they and their physicians really believe is suboptimal, but we certainly could collect clinical endpoints in a rigorous way, in the kinds of studies that we're talking about. It appears that these are very advanced patients, in which there is going to be not only risk of important clinical endpoints--both those reflecting toxicity and efficacy--but in some cases mortality. And I believe that that information could be useful for two purposes: one is it would allow us to compare both the people that got the new drug--tipranavir, in this case--right from the

start, and those who were delayed, and some, of course, who are getting it in a delayed fashion may not get it at all, so it would allow us that information. It would also allow us better to relate some of the markers that we have to the ultimate clinical endpoints that we're concerned about, so that we could go back and put together all the salvage studies that we have--I know this is a big undertaking. I wish there were a simple way to do it.

But I think if there were--if we could put together all the information that we can from salvage studies together, we could better understand what the meaning is of some of the short-term markers on longer-term benefit; and also identify the important predictors--as we've talked about today, both predictors for efficacy and for toxicity--to really pion them down as well as possible to see how well we can classify patients from the start.

Obviously, it's a lot easier not to do those things. But the question is: if we don't do

them, are we ever really going to get the truth about the impact of these drugs on patients' health and well being.

DR. ENGLUND: Thank you. With that I'd like to ask members of the Committee questions about the indication that they would recommend this drug to be used for. And I'm supposed go and retrospectively say that Dr. Jeff Murray, who spoke, was the Deputy Director of the Division of Antiviral Drugs. Just--I'm sorry, that's late.

Questions on indication. We voted--as a committee we voted yes. Who should we be recommending this to be used for.

That's you question, Dr. Birnkrant--correct?

DR. BIRNKRANT: That's correct. We're interested specifically in the patient population for the indication.

DR. ENGLUND: I think it's been clearly stated, at least on this side of the table--and the non-voting side of the table--that it needs to be used for those who have advanced disease and

failure of other available--and actually some of us voting people--those patients who have failed available first-line and even second-line protease inhibitor therapy.

Could we have some other issues?

Dr. Miller?

DR. MILLER: Yes, I don't think that necessarily they need to have advanced disease. I think you can have failed several protease inhibitors for whatever reason, and not necessarily have advanced disease. So I would make that distinction there.

DR. ENGLUND: Would you say solely "failed other--"

DR. MILLER: Yes. In my opinion, the disease state should not come into play here.

DR. ENGLUND: Okay.

DR. ENGLUND: Dr. Grant.

DR. GRANT: I think the data mainly bears on patients with protease inhibitor resistant virus, rather than protease inhibitor experience, per se. And I guess I wouldn't expect this drug to

be used in someone who had wild-type failure of protease inhibitors in the past.

And so--you know, I guess I would recommend the indication be written in terms of PI resistance, rather than PI experience.

DR. MILLER: Can I just make another comment on that? I think that's actually very good, because the patient could have also been infected with a protease-resistant virus, so not necessarily be experienced. And that would still be the same.

DR. ENGLUND: Dr. Munk?

DR. MUNK: Yes, that was really the point I was going to make, is that I don't protease inhibitor treatment-experienced is appropriate or adequate, but it should really talk about protease-resistant virus, or multiple protease-resistant virus.

DR. ENGLUND: Do you want to specify tests here? Anyone?

Dr. Gerber.

DR. GERBER: Yes, I mean, I think what we

really are saying, that before you start somebody with tipranavir, you need to have genotypic and phenotypic testing, number one to make sure that the patient is still susceptible to tipranavir. Because if it's a 30, 40-fold reduction to tipranavir susceptibility, this would not be the drug you'd want to use; and also to be sure that that is the only option available--for example, if you have a two-fold reduction to amprenavir, then you might choose another direction.

DR. ENGLUND: Dr. Maldarelli.

DR. MALDARELLI: Yes, I think getting both of the tests at the beginning may be--it may be a little bit of overkill. I think if you got the genotype first and noticed that it had any of those key mutations--82, 84, and perhaps 90; I don't think there will be a lot of 33s at baseline--then that might be something you wouldn't anticipate using it in those patients.

So, in other words, the entry criteria for this trial is really all the data we have that's useful. There are no clinical--as nearly as I

could tell, there were no break points defined by this trial or any of their others.

DR. ENGLUND: Dr. Grant.

DR. GRANT: Yes, I agree that either a genotype or a phenotype would be adequate. And I wouldn't specify the test or the exact interpretation of what "resistance" is, because that actually evolves fairly quickly, and you wouldn't want to tie this indication to the current interpretation of those tests.

DR. ENGLUND: Dr. Miller.

DR. MILLER: I just had a question: to what extent, if a resistance test requirement is included in the label that mandates how the drug is used across the different programs--like the ADA programs and, you know different situations. You know, I just don't know to what extent resistance testing is, in fact, being reimbursed, and whether that would limit the access of patients to this drug?

DR. ENGLUND: Well, I can tell you as a practitioner that if it's not required I'm going to

have trouble potentially getting funding for it through my state. So--I'm sure it varies.

Any other experience? I know it's hard.

DR. MUNK: Just the fact that it is required doesn't guarantee it will be reimbursed.

DR. ENGLUND: Absolutely. And I guess I would consider that requiring both genotyping and phenotyping might be a problem.

VOICE: [Off mike.] [Inaudible.]

DR. ENGLUND: Sure, Doug--Dr. Mayers?

DR. MAYERS: We struggled with that issue ourselves, with labeling. And I can tell you we've surveyed 30 of the 50 states already, and 13 of the states do not support resistance testing of either genotype or phenotype.

DR. BIRNKRANT: We appreciate the input we heard about the indications. So we're comfortable moving on.

DR. ENGLUND: Good.

[Laughter.]

Question 2--we have really discussed this at length, and we have--we are so fortunate to have

our hepatologist panel over there to give us some ideas. And I'd specifically like to hear from them.

For Question 2 it says:"Given the data on transaminase elevations, please provide your recommendations for TPV/ritonavir use in patients with underlying liver disease, monitoring and management of hepatotoxicity, and future studies."

Now, since some of you were "no" voters, I would really like specific indications on future studies that you really think that we need--as well as the other bullet points.

Dr. Sherman.

DR. SHERMAN: So, the problem with transaminase elevations and how they've been used in the past is that they are, at best, a surrogate marker for current activity. And what they don't reflect is actually the disease that's been; the fibrosis in the liver.

And at the end of the day, in most patients, except those who develop fulminant hepatic failure acutely from a virus, or a drug, or

some combination, the issue is really not the acute injury. It's what happens over time, and in what milieu that occurs, because patients over time develop fibrosis, develop portal hypertension. And it's the physiologic changes associated with altered blood flow that, at the end of the day, make the difference in defining what we call end-stage liver disease.

This is a really tough question. We could take a page from what's been done with other hepatotoxic drugs that are in common use--for example, methotrexate, by rheumatologists and by dermatologists for treatment of psoriasis. And what they basically say is: if liver enzymes are normal at the onset, then you monitor those patients. And at some point down the road--and there are recommendations that many, if not all, patients need a staging liver biopsy to see what's going on.

And if patients have abnormalities at baseline, then those should be evaluated at that time, before a drug is initiated, to become part of

the decision process.

And in this setting, many of the patients that have underlying or baseline liver abnormalities are going to already have them because of presence of hep B, or hep C; perhaps they're already on some hepatotoxic agents. Recommendations already exist that patients with chronic and hepatitis and hep C should be biopsied for evaluation. And recommendations exist that patients with abnormal enzymes, and replicative hepatitis B should be biopsied and evaluated.

So, if you take those out and say, "Following the rules, those patients should be biopsied anyway, before you make a beginning decision--"--and, by definition, "chronic hepatitis" is defined as abnormal liver enzymes for six months or longer--something that's been long ignored in the ID community--I think that if you can document that liver enzyme abnormalities have been present--again, a baseline liver biopsy is mandated.

And with that information, looking at the

degree of disease activity at baseline, looking at fibrosis that's present on an individual patient basis, a risk-benefit ratio can be assigned.

Unfortunately, at this point we don't even have the data that tells us that the patients who have advanced liver disease are the ones at greatest risk for long-term injury. And that's a study that should be done--perhaps following liver enzymes in patients where biopsy criteria at different stages are know; a cross-sectional analysis that follows forward prospectively.

But, you know, we do now have guidelines and recommendations, for example, that say that in a patient who is being treated with an agent like ddI, which is relatively contraindicated with an interferon ribavirin--particular the ribavirin--is added, that the patients that are at greatest risk are those who have more advanced liver disease. Those are the ones that tip over and decompensate and go on to end-stage liver disease.

So, in terms of guidelines, I would say: biopsy patients who have abnormal liver enzymes--as

is appropriate for the work-up of patients with abnormal liver enzymes. And, on an individual patient basis, based on degree of fibrosis and the severity of their HIV disease, in the setting of drug resistance, make a decision about initiation of tipranavir.

DR. ENGLUND: You're next--yes, Dr. Rodriguez-Torres.

DR. RODRIGUEZ-TORRES: Yes, I agree a hundred percent with Dr. Sherman.

But in terms of specific studies, a study in hep C co-infected patients, with pre--and biopsies along the way, prospective, will be fine.

An idea--I don't know if the sponsor can consider a large, more loose follow-up of ALT of patients that are entered into treatment, like requiring baseline at least a minimal work-over; hep C, hepatitis B--and then follow, as the physicians that treat the patients to report ALT elevations and probably consider biopsy later on on the treatment. That's another idea that could give much more information.

DR. ENGLUND: The representative from Johns Hopkins?

DR. SULKOWSKI: I wanted to make a comment

on some of these issues, because I'm unique, in that--

DR. ENGLUND: Could you identify your name, please?

DR. SULKOWSKI: Dr. Sulkowski, from Johns Hopkins.

I wanted to make a comment on this issue of the treatment of patients with underlying liver disease, because I'm a person trained in infectious disease, who's spent the last 10 years working on liver disease. I think the perspective is this: that in a patient with few, if any, drug options for HIV treatment, in that context, we really are in the pre-HOT era, where liver disease is not the driving mortality. And that's true of many cohort studies. It's still true of our patient population.

The second thing I wanted to say about antiretroviral toxicity is it is not by any means

unique to this particular agent. In our clinical cohort, among naive patients starting their first PI, 12 percent develop Grade 3, 4 liver enzyme elevations. If they're hepatitis C or B infected, that number goes up to 15 to 18 percent, develop Grade 3, 4 liver enzyme elevations.

It's certainly not my intention to minimize this signal that's been seen in the RESIST 1 and 2 trials, but I would comment that this is a situation that clinicians--at least in east Baltimore--have seen before with other drugs and, with appropriate guidance, can deal with very well.

I'm concerned about the discussion of liver biopsy--although, clearly, I think it has a role in the work-up of ALT--it's simply not accessible for many patients. And, clearly, it's part of a risk-benefit assessment.

So I wanted to get back to this question about risk-benefit, because that's why I think we need to talk about this.

Thanks.

DR. ENGLUND: Dr. Munk?

DR. MUNK: Yes--to kind of pick up on what Dr. Sulkowski was saying, I think it's unreasonable to put the whole question of liver impairment and

prognosis under HIV treatment on this one drug, and this one sponsor. And it's something that I really hope the FDA will carefully consider how to examine the broader issue: how do we deal with co-infected patients?

What kinds of studies are needed? And there are probably going to be multi-manufacturer, multi-product studies to really get some answers--about liver impairment; how many times should we biopsy? Which patients are at highest risk for decompensation--and so on.

DR. ENGLUND: Thank you.

Briefly, to summarize, I think that there's some concern that the hepatitis and increase in liver function enzymes that were seen in these patients can be a problem in a subset or minority of patients. How specific it is to tipranavir in this highly treated patient population perhaps is not so clear.

The concern of transaminases as a reflection of the true liver function perhaps is worthy of further follow-up. And I think everyone is concerned that at least the patients enrolled in this study--and others--need long-term follow-up to help the clinicians know how to deal with these

type of patients.

And that's probably not a very great summary.

Do you have an additional summary?

DR. GERBER: No. I have an additional comment.

Although we keep talking about, you know, liver problems associated with using antiretroviral therapy, but this study had a comparator arm. And the hepatic abnormality with tipranavir was twice as bad as the comparator arm. So we have something to compare them to.

Now, if the reason the comparator arm didn't have hepatotoxicity is because nobody was taking the medications, that's one thing. But if it's truly--if I'm to believe that there was very

significant adherence to this therapy, this would indicate that this drug is more hepatotoxic than the comparator PIs that are available on the market. That's the way I interpret this.

I could be wrong in my interpretation, but that's way I would interpret that.

DR. JAMES: Dr. England, can I say something quickly? I'm sorry--do you want to go first?

I just want to echo that statement and remind everybody that it wasn't just tipranavir against the comparator arm. Remember, we had 19 percent liver toxicity seen in healthy normal. So this is not just a signal in HIV-infected patients who get a protease inhibitor. These are healthy people, baseline normal LFTs, and they have abnormalities after taking tipranavir--some of them six days' worth of dosing.

So I think that's significant.

The other thing I just wanted to have you all comment on is specifically your thoughts about using tipranavir in patients who are co-infected at

baseline--so what your thoughts are on hepatitis B and C patients' getting this drug.

DR. BIRNKRANT: So, more directly: is there a patient population with liver disease in whom you would not use this product--for the record?

DR. SHERMAN: May Dr. Sherman try?

DR. ENGLUND: Dr. Sherman?

DR. SHERMAN: Okay. As Dr. Sulkowski indicated, his studies and others showed that with initiation of most antiretrovirals, those patients that already have underlying liver disease, including hep B and hep C, are at greater risk of developing enzyme abnormalities that we associate with ongoing hepatotoxicity. And we don't exclude those patients from being treated.

In terms of the issue of the hep C specifically, there are no data. The sponsor indicated that they plan on moving forward and looking at interactions with interferon and ribavirin which today is the standard therapy. The agency approved PEG interferon alpha-2A and ribavirin for treatment of co-infected patients

just a short time ago. And so it is critical to know what interactions may be present before making the decision to embark on such therapy.

Patients who are sitting, though, with very, very low CD4 counts are probably not going to be patients they're going to candidates for that therapy initially. But if they respond, we're going to need to know that answer, because we're not going to take them off, then, their regimen containing tipranavir to treat them with interferon and ribavirin.

So, I think that it this stage, the jury is out. And that's one of the earliest study that the sponsor is going to have to deal with.

All of these are risk-benefit assessments. And I think that they come down to risk-benefit assessments in individuals. And to agree with and still disagree with Dr. Sulkowski's comments before, you look at each patient. A patient who has multi-drug resistant disease, whose CD4s are low but not critically low, who doesn't yet have severe opportunistic infections--you'd really like

to know where you're at before starting a potentially hepatotoxic agent. And that patient--if they had cirrhosis, you might choose to delay.

And I think it still comes down to clinicians and patients making individual decisions. And somehow that's going to have to be emphasized in the labeling.

DR. MORSE: I just wanted to add one thing that hasn't been mentioned, and that is: in a few of those slides there was a suggestion that there's a concentration relationship with hepatotoxicity. And if you believe that data is strong enough, and it's possible that certain elevated concentrations may make hepatotoxicity occur more frequently or occur more severely, that certainly follow-up studies would need to clarify that relationship, because it seems like it was already present in the preliminary studies.

DR. ENGLUND: Dr. Kumar?

DR. KUMAR: I want to make--from the practical standpoint--Dr. Sherman, I hear very well

what you said about the liver biopsies. But from the practical standpoint, it will be impossible for us as clinicians to get liver biopsies on people with mild abnormal liver enzymes.

I recognize that clearly there are concerns about hepatotoxicity, but when we translate it into the clinical world, if we are required to get a liver biopsy before we can initiate this drug, we just will not be able to use this drug. That's just from the practical standpoint.

And we have had many other drugs that are hepatotoxic. And what we have done as clinicians is, once we have recognized that they're hepatotoxic agents what we do is we monitor patients, both clinically and with lab measurements, using a combination of both. And I can't see why we could not do the same thing for this agent.

There are other drugs--including nevirapine, which clearly is hepatotoxic--and the way we manage that is we have recognize who--for

which group of patients it's hepatotoxic, with clear parameters on how to monitor them. And I would think, from the clinical standpoint, if the agency approves this drug, that is the way we, as clinicians, would like to monitor it.

DR. ENGLUND: Ms. Dee?

MS. DEE: Thank you.

I'm just wondering--I've often been accused of having perseverance. Given all of the reasons why we can't make all of these qualifications in the indication and get any use out of this drug practically, again I would like to know for the record what authority the agency has to say to any sponsor: "Look--"--other than a black box label or something in the label.

Is there something that the agency could make them do to educate physicians about the high risk for liver disease, or the drug interactions.

I mean, what is it that we can do to get this news out widely ahead of time instead of waiting to hear it on the news.

DR. ENGLUND: Dr. Birnkrant first.

DR. BIRNKRANT: One thing we could do is we could negotiate with the company and reach an agreement, and then put that agreement into the

letter that they would receive when we make our regulatory decision. And in that way, that would be binding.

DR. ENGLUND: Dr. Kuritzkes?

DR. KURITZKES: Daniel Kuritzkes, Harvard Medical School. A quick comment on the issue of the comparison in hepatotoxic events between the tipranavir arm and the comparator PI arm.

There's no doubt that tipranavir causes hepatic toxicity. However, I don't think the RESIST studies can be interpreted as randomized comparisons of the risk of hepatotoxicity between tipranavir and the comparator PI arms.

Recall that investigators were asked to select a drug that the patients would take, and the patients had to be on a failing protease inhibitor, and they had to have essentially normal LFTs--less than Grade 2--to get in. And you'll recall, as well, how many patients remained on the same

failing drug.

So, in essence, you selected against pre-existing toxicity, or known toxicity of the available protease inhibitors. And so there is a kind of an inverse bias against finding toxicity in the comparator PIs.

That doesn't minimize the fact that hepatotoxicity occurs with tipranavir. It's just that this is not a randomize comparison of risk of hepatotoxicity between existing PIs and tipranavir.

DR. ENGLUND: Last comment on this question.

Dr. Rodriguez-Torres.

DR. RODRIGUEZ-TORRES: To answer specifically the question that Andrea, I think, asked, I won't say that hepatitis C or B co-infected patients should be omitted from enrollment in treatment. But certainly those with moderate to severe fibrosis shouldn't receive therapy--and as Dr. Sherman says, if I have in front of me a VIRCO test of a patient that qualifies for this drug, but she happens to have

400 CD4, and is actively employed, and no complaints, no symptoms.

It's a different story with this patient as with somebody that has 5 CD4, that is at the end of the road. So you have to consider that.

For this patient hepatotoxicity is much more important risk than for somebody that doesn't have anything else.

DR. ENGLUND: Okay--Dr. DeGruttola.

DR. DeGRUTTOLA: Yes, a quick response to Dr. Kuritzkes' comments.

I agree that, as he said, because you're specifically selecting patients who are doing well on their current protease, that the comparisons of the amount of liver abnormalities on the tipranavir compared to the control arm are biased in the direction that he mentioned.

However, I would say that since this is how tipranavir might be used to make a decision whether to switch a patient onto the new agent, tipranavir, or keep them on the proteases that they're currently taking--or the regimen that

they're currently taking--or making some other change that doesn't involve tipranavir, that comparison may actually be what's relevant, in terms of making the decision--even though it isn't the unbiased estimate of the effect of tipranavir compared to another drug.

DR. ENGLUND: Okay. Thank you very much.

I'd like to move on to Question 3. And, Dr. Birnkrant--

DR. BIRNKRANT: Actually, I'm sorry to delay that. We still need input with regard to monitoring and management.

So, in other words, do we monitor at baseline? Week 4? Week 8? Week 12--and periodically thereafter? Could someone propose a monitoring scheme for us?

DR. ENGLUND: Dr. Fish.

DR. FISH: I can tell you how would envision seeing myself doing this in the practice.

I would look at the entry criteria that you used for the study. So I would not start someone who had more than Grade 2 elevations in

their liver enzymes. And I probably would monitor them every other week, personally, in the beginning, if they've got underlying liver disease. To me that seems not particularly burdensome--perhaps even weekly if I were extra concerned, but certainly every other week would seem reasonable.

I would also avoid it in patients whom I suspect have clinical cirrhosis. It is true that we are not able to biopsy all of our patients with LFT abnormalities. We are fortunate in New York that we are funded such that we can often get biopsies. But in many states your patients on ADAP, your patients on Medicaid will not have a liver biopsy available to them.

So, I may have a normal AST or a normal ALT, but their albumin is 2.5, and their platelets are 75,000, so I'm going to suspect that they probably have a significant amount of liver disease, and the company--the sponsor--talked about doing studies in patients with chronic liver disease, including compensated cirrhosis. So we

would await that data.

DR. ENGLUND: Anyone else?

DR. WOOD: I would just maintain that since we saw the Kaplan-Meier showed that showed that there was continued increase in the incidence of hepatotoxicity, that it be reinforced that, in addition to very vigilant monitoring--initially, following the start, every two weeks, then every month--that vigilant monitoring would have to continue as long as the patients remained on tipranavir. At a very minimum, you know, maybe after Week 24, at least every two months. Because the issue is that there was still a continuing incidence of increasing liver transaminases.

DR. BIRNKRANT: Okay, that's fine. We can move on.

DR. ENGLUND: Do you want us to address Question 3? Have we discussed that already? I think we could go on at great length about Question No. 3, but we have specifically addressed this.

DR. BIRNKRANT: Well, if the Committee is comfortable with what was discussed already, we can

move on to the next question.

DR. ENGLUND: The question is: increased incidence of rash in females--please provide your recommendations.

It's been recommended by multiple people that we need more information--urgently.

Dr. Miller?

DR. MILLER: I was just going to make one additional suggestion, and that is in HIV-positive women, now that the epidemic is aging, there's the opportunity to also look at this in older women who may not be on birth control, and so that that may be a good population to actually look at also.

DR. ENGLUND: Thank you.

Dr. Wood?

DR. WOOD: Just one more comment. Thank you.

I do think that there would need to be a recommendation in the labeling, to clinicians, regarding how to manage individuals who developed rash. Whether there's a recommendation once the rash develops--since--I think the encouraging news

is that there was no evidence of Stevens-Johnson, EM or TEN associated with the rashes that were described in the studies presented.

But--I think there are going to need to be recommendations regarding do you continue to just press on and treat through, or is the official recommendation that tipranavir be discontinued upon the development of rash?

DR. JOHANN-LIANG: What happened with the issue of women taking tipranavir at this time--before these studies are done? Somebody had brought that out. We just want to be clear--part of the inclusion--the indication.

DR. WOOD: That women can take it?

DR. JOHANN-LIANG: Yes. I think the need is, is that we would--even though there clearly is disappointment, in that there is not more data regarding toxicity, and viral efficacy in women, I think it would be a real disservice--particularly given the heterosexual nature of the epidemic in this country--to deny access to tipranavir to women at this time. So they definitely should have

access to the drug.

DR. ENGLUND: But I would just like to say, after being on this committee for four or five years, I'm getting to the point where I'm ready to not allow this drug to be licensed because of the lack of availability in women.

I mean, this is a recurrent, recurrent, recurrent theme. And I think that it's--we don't want to discriminate against the women. On the other hand, I think that manufacturers need to be actively recruiting women in studies like this. You can't just go to a clinic and enroll whoever shows up.

So I would like to recommend that strongly.

MS. DEE: Just very quickly--and how many women do we think are going to get on this study now? This rash study, now?

I think--you know, maybe they missed their chance on this.

DR. ENGLUND: Well, they are doing studies in naive people--which should include women.

MS. DEE: But I'm just saying the minute--if I was a woman, I may not want to get on this--number one--and number--I am a woman, right?

[Laughter.]

[Laughs.] And, number two, you know, if I started to get this rash I might think--you might see the back of me pretty quickly. You know, you might not be able to get a chance to--you know, "Can this be treated through?" or whatever.

I'm just saying they may have missed their chance to characterize this better.

DR. JAMES: Just to let you know, the naive study is fully enrolled, and it's about 20 percent.

DR. ENGLUND: Dr. Birnkrant? Anything else?

DR. BIRNKRANT: We can move on.

DR. ENGLUND: To move on--Question Number 4, which basically is an opportunity for those around the table to discuss post-marketing drug interaction studies. I think this is a very important point.

"Current information indicates the next

effect of tipranavir/ritonavir and substrates of CYP 1A2, CYP 2C9, 2C19, and 2D6 is not known. The competing effects of tipranavir/ritonavir on CYP 3A and P-gp.

"Please comment on additional post-marketing drug interaction studies."

I think this is really an important part, and I'd want to make sure, especially, that the far right-hand side of the table--our pharmacology end of the room--can speak up here. Everyone gets to speak up, but we value your opinion.

DR. BIRNKRANT: So, for the record, we need to hear whether or not additional post-marketing testing, with regard to drug interactions, needs to be conducted.

If so, then which drugs?

[Pause.]

DR. ENGLUND: I'll call on someone.

[Laughter.]

Dr. Hall--has volunteered.

DR. HALL: Oh, I think an excellent first step is the one proposed by the sponsor, which is

to conduct a cocktail study which would essentially mean administering a whole bunch of probes for the individual cytochrome P450s, and obtaining a lot of information in one single well-conducted study that would tell them if the 1A2, 2D6, 2C9, 2C19 enzymes were going to be significantly affected.

So I think that's an excellent approach that they have suggested. Of course, the devil is in the details--which we didn't hear much about. And perhaps they could comment a little on that.

One of the components that they proposed was to include a P-gp probe as part of the mixture, which is also an excellent idea in the context of their hypothesis that the interactions with the other protease inhibitors were mediated by a P-glycoprotein effect--which we all have to understand is just a hypothesis, and it's not based really on anything substantial.

So, to actually take a well-characterized drug such as digoxin, for example, as a probe of that would be an excellent approach, I think.

And the value of these studies is to

provide some kind of mechanistic understanding so that we would be in a position to attempt to extrapolate to the hundreds of possible drug interactions that are out there, and perhaps take the burden off conducting every single interaction that somebody could think of.

I think one of the components that would be important for them to look at in their studies would be whether the liver and the intestine activities of the enzymes and the transporters are being affected. This is also going to add a lot of mechanistic insight, and should improve their ability to predict drugs that are not specifically tested, once they've completed this study.

So, if they have some details on that, I think it would be very instructive to hear of it. I think it was mentioned that it was getting ready to start, and I'd be curious to hear how they're going to design such a study.

DR. ENGLUND: Dr. Capparelli?

DR. CAPPARELLI: I'd just like to echo the idea of working forward from a mechanistic

standpoint, in addition to the design of having the commonly used agents looked at.

As soon as you get beyond even a two-drug combination, it gets complicated. But I think understanding where these interactions are coming from is extremely important.

So, in looking at the probe, digoxin may not be a common drug but, as was mentioned, that would be one that could be given. And looking at it both orally and IV would give insight into exactly where things are going on.

And I think that we really need to differentiate between those so that we can understand where these interactions are coming from.

I think that some of the data that was presented earlier in regards to the proton-pump inhibitors was helpful. And sort of maybe a screening approach--whether or not it's a full population, or just to get an idea of where some issues might be--is a good thing to do.

I also think, from a mechanistic

standpoint, some of these things can be looked at in preclinical settings, like with a knockout model, so that some of the P-gp interactions--there are knockout mouse models that one can look at. And they should be interested in those aspects, as well as recognizing that when we're thinking about transporters, there's more than just P-gp. And we may have--you know, it may be a transporter that hasn't been mentioned here at all, in terms of the MRPs.

So I think we need to make certain that we aren't missing those components.

And, linked to that, one thing that wasn't mentioned at all is if anyone's looked at any of the genotype information. There are some polymorphisms. What their functionality is is still being understood.

But I think that incorporating some of that in some of these drug interaction studies--especially the more well-controlled studies--is going to be important.

And then lastly, for the protease

inhibitors that have been tried thus far, I'd be interested to hear if there's been any protein binding studies. You've got drug that's extremely highly bound, in high concentrations relative to the other drugs. And what we may be seeing may be due to transporter, but it may be due to displacement if the free drug concentrations aren't changing as much as, maybe, the total, it may impact how we want to use these drugs in combination. Although it does complicate the assessments.

DR. ENGLUND: Any other suggestions from the Committee?

Dr. Morse?

DR. MORSE: I agree with the things that were presented by the company. And I certainly agree with the idea of looking at SNPS. I think this is one of the first drugs I've seen where drug interactions are actually explained by the induction of P-gp activity in the gut. So that was very interesting.

I just wanted to follow up a little bit

more on the idea of dual protease inhibitors, because I think in this patient population I would not really give up.

To me, the negative interactions that were observed can probably be overcome--maybe with a little different study design, where patients are maybe in a GCRC, and some dose escalation is done with the second PI to find out what dose of that second PI could then actually be given with tipranavir.

So, although there were negative interactions, I wouldn't give up on that.

DR. ENGLUND: Comment from Dr. Capparelli?

DR. CAPPARELLI: Yes, there's one interaction that wasn't mentioned, and it may come out--they may have information on it already. But that has to do with tenofovir. Again, it has activity on the transporters. It was used a lot in this trial, and you may already have this information.

But I think that's something that should be looked at, given its interaction with other

protease inhibitors.

DR. ENGLUND: Dr. Sherman?

DR. SHERMAN: I'd just like to put in a plug for beginning to investigate the interactions with calcineurin inhibitors, and with IMDPH inhibitors like MMF, that are used in the setting of transplant. Because if we get the virus under control with this and combination of other agents, and if we have increased liver toxicity, we'll be thinking about transplant.

DR. ENGLUND: Dr. Gerber.

DR. GERBER: Yes, I just want to re-stress the importance of statin interactions. And it's not predictable. You can give a cocktail all you want, and identify the cytochrome P450--and let me just give you an example. What was studied in the ACTG was the interaction between efavirenz and statins. And pravastatin, which is not a substrate for cytochrome P450 3A4 was reduced by almost 50 percent by efavirenz--totally unexpected.

So I think drugs that are going to be commonly used with tipranavir should be studied.

And we don't know all the information, for example, how a drug is eliminated, or what transporters are being used. There's a whole bunch of transporters that we're not looking at.

And so drugs that are very commonly going to be used in combination I think should be studied individual. For example, phenytoin would be also a good example. That's commonly seen in the clinic. Valproic acid--etcetera.

DR. ENGLUND: Dr. Fish.

DR. FISH: It may be too late to do anything about this particular drug, but a concern that's clinically relevant for our patients--be it tipranavir or any other protease inhibitor--is midazolam. As our patients go for endoscopy and, increasingly, as they become age 50 and older, we're doing screening colonoscopies--many of the endoscopy units only have midazolam available.

So our patients are getting exposed to this drug, and yet it's on the contraindicated list. It's probably the most frequently used short-acting sedative that is given in endoscopy

centers and probably in hospitals for conscious sedation.

DR. ENGLUND: Dr. Hall.

DR. HALL: I think you could be in luck there, because I think the cocktail that could be used would include midazolam. And so it could, you know, solve two things with one study, then have a specific answer to your question, as well as provide a general answer as to what the CYP 3A enzymes are doing.

DR. ENGLUND: Dr. Birnkrant, we've give you a nice long list. Do you want more?

[Laughter.]

DR. BIRNKRANT: I think we're saturated on that one.

DR. ENGLUND: Okay. We can move on.

Okay, I'll just summarize that we had input from the committee, basically emphasizing their agreement with the cocktail study, involving the mechanistic approach and also specific drugs--with a broad range of issues.

Now, for Question No. 5--Dr. Birnkrant, do

you want a vote on this? Or just a discussion?

DR. BIRNKRANT: I think we were hoping for a brief discussion based on the information on the biomarker that we presented: the Cmin over IC50. And Boehringer Ingelheim presented information on C trough levels.

I guess a general question would be: is it worth exploring further uses of biomarkers to determine whether or not therapeutic drug monitoring would be helpful--with this drug and in general--in a salvage population?

And we'd like a discussion, because not only do we have Boehringer Ingelheim here today, but we have many pharmaceutical companies in the audience, and it may be pertinent for them to hear the discussion, as well.

DR. ENGLUND: Dr. Grant--the question of therapeutic drug monitoring, with this specific example here.

DR. GRANT: Well, I think the concept is promising, but it would be very premature to recommend using these strategies for monitoring

therapy at this time. We have to keep in mind that in order to do this well, we need three things, really.

We need, first of all, a validated protocol for collecting the specimens, which includes the definition of when they should be collected. And during these studies there was a broad range of times used.

In addition, you need assays for measuring the drug level and interpreting the drug level with respect to protein binding that are validated and have well characterized performance characteristics.

In addition, the phenotypic assays, I think, are all valuable but, to my knowledge, none of the phenotypic assays have been fully evaluated with respect to their performance characteristics--at least not in the public domain.

And so I think it would be premature to propose that this is ready for management of individual patients at this time.

Having said that, I think the concept is

promising, and it bears not just on tipranavir, but all of the PIs, I believe.

But it would require, you know, really extensive validation of all three of those components of this calculation: the timing of the specimen; the drug resistance phenotypic assays and the drug level assays, as well as adjustments for protein binding.

DR. ENGLUND: Dr. Morse.

DR. MORSE: I think I'd agree with one out of those three. I think the--I'm not sure if the issue of protein binding in the context of therapeutic drug monitoring would be an essential component in order to interpret a concentration.

The assays and the ability to do this, I think, is in place--in a clinical trial sense. I agree it's not in place for all patients everywhere.

ACTG is currently conducting a study that's got 30 centers with therapeutic drug monitoring.

So I think do-ability is maybe not the

only concern. Since you did mention there's other companies in the audience, I'll say there's a general lack of enthusiasm for having therapeutic drug monitoring. It makes things more difficult, and is not viewed that positively.

Having said that, based on the data I saw, if I was a patient who probably had a cutoff greater than 3, and if I had some other reasons for being concerned about taking tipranavir, I'd want to know what my concentration is in relationship to susceptibility.

Having said that, the other item I agree with is that a lot of places don't have phenotype results. So you wind up with mutations--and there is actually some data that have developed something called a "genotypic inhibitory quotient." There's also the VIRCO Virtual Phenotype. So there are ways to get numbers for that denominator.

So I think what I'm saying is that I totally agree: it should not be a requirement to use this drug. But I do agree there are certain patients that might take this drug, where studies

of therapeutic drug monitoring might be able to identify if an outcome can be enhanced, or a toxicity avoided.

DR. ENGLUND: Ms. Dee?

MS. DEE: I'm not sure what needs to be done for therapeutic monitoring for everybody to feel happy with it. I don't think the companies are going to be excited about it, and I don't think they're going to do it unless they get some message from on high that it might be a good idea.

I think, from a patient perspective, really about time that we started to explore when it's useful, and if it's useful. I know there are plenty of people in the community--I mean, they do it in Europe pretty much--it's accepted there as part of the standard of care.

And I think that there are many people in the community that would really like to know whether it would be helpful to them to monitor their levels. And if there are drugs that will work for them--if it's just a question of adjusting doses--that they'd like for this area to be

explored.

DR. ENGLUND: From the sponsor. Identify yourself, please.

DR. SHAPIRO: I'm Jonathan Shapiro. I work at the National Hemophilia Center in Tel Aviv, and Stanford University. And I'd like to comment on TDM, since I have been on the other side of the Atlantic doing it for a number of years. And I think it's a very interesting concept.

I would caution--and I think we've learned this from other new diagnostic modalities--I think that we've seen very well correlations--as we did today. Wonderful work by the agency and by the sponsor--that the correlations between drug levels, exposure, toxicity; the interaction between resistance and pharmacology, where we get IQs--these correlations have bene shown very nicely for many protease inhibitors. And I think it's very comforting that we're seeing this again her.

The challenge has been, over the last five or six years, turning this into a useful clinical tool, and also making sure we don't damage our

patients. Just maybe commenting on the protocol suggested by the agency, which I think would be maybe interesting for a study--how you actually do that, I can tell you from my practice--how, at two weeks you determine if the drug is tolerated, based on--you know, we know here that you can at two weeks--how would I determine if now this patient is tolerating this drug and I can safely increase it? And if I increase it, how do I increase it? And when do I measure it again?

These practical things have led--at least on the other side of the Atlantic--also to negative outcomes. If you're not sure what you're doing, and this was not included in the study, at two weeks to start increasing the dose before you're sure what toxicity there is and how to monitor it would be dangerous.

In addition, reducing dose of drugs--for example, something that we've discussed before--for NRTIs, when we see toxicity in high levels, to actually reduce the dose of, let's say, efavirenz to half, as a clinician is something which has not

been studied.

And there's dangers of putting out technologies that have not been studied.

So, although I'm a proponent of TDM, I think the right way to do it is through studies. I think the ACTG has taken on this challenge.

I agree with you that the companies should absolutely be forced to play ball--whether it's the ACTG or other large investigators. But I would be very cautious about doing TDM without having first proven how to do it right, and that it has utility.

Thank you.

DR. BIRNKRANT: We recognize that, as well. And we also realize that the assays that are available today should not impact the approval of this product.

But what we'd like to get feedback on is: what type of trials should we be asking Boehringer Ingelheim and others to do with regard to therapeutic drug monitoring.

So we're asking a critical trials question: in the next clinical trial, what should

we be asking the companies to do? Should we do these concentration controlled studies? How should we do them--etcetera.

DR. ENGLUND: Dr. Gerber?

DR. GERBER: Yes. These are very difficult questions that you're asking. And I was surprised--

DR. BIRNKRANT: Thank you.

[Laughter.]

DR. GERBER: That's your job, right? I was surprised to hear Dr. Shapiro, who I've had numerous arguments with about TDM in the past--

[Laughter.]

--but I think what I see a potential of doing a trial is maybe reducing toxicity. Because essentially almost all the trials that have looked at--or a TDM where it's been most useful--has been in reducing toxicity.

And I've reviewed TDM for probably 20 years for different drugs--obviously not HIV drugs. And, really, the most useful aspect is to reduce toxicity.

What I saw in the data that was presented, that there was clearly a concentration-toxicity relationship--especially hepatotoxicity, where at

certain concentrations, although it was a continuum, which always makes things very, very difficult.

So if there was a way to design that if your concentration is about a certain--but then you always have a question: what happens if your concentration is changing? How many times do you have to do TDM? And when are you going to get to a level where it may not be efficacious any more. So you get into problems with resistance. So those are all extremely complex issues.

I've been generally very much against TDM because of that--not to mention the fact that laboratories that offer TDM frequently don't have the quality control, and they've not undergone proficiency testing necessary that I would feel comfortable that what they're telling us the level is is correct.

But I think reducing toxicity, if it could

be designed in a reasonable way, might be something to look at.

Efficacy-wise, I think it might be a little bit more difficult to do, because it would clearly require either phenotypic or Virtual Phenotype to know at what level of susceptibility you have. And then, as we heard, that's not offered universally.

But for toxicity, if you can identify a concentration above which there are going to be clearly high percentage of patients who develop hepatotoxicity, that would be something to look at.

DR. ENGLUND: Dr. Maldarelli?

DR. MALDARELLI: I think I'd have to have some concerns about making any recommendations based on what I've heard and what I've seen in my experience in doing TDM at NIH. I think it might be a little bit difficult, even in the sense of looking at toxicity.

The data that was presented today, I agree, had a linear relationship between C min and percent of patients with ALT toxicities. But that

line has a fairly shallow slope. And the five points that determined it probably have a much larger standard deviation.

So making a firm recommendation based on this I think is somewhat--I think is difficult. And the data involving inter-patient variability makes it even more problematic.

So I think making a firm conclusion today, based on what I've heard, I'd have a hard problem.

DR. ENGLUND: Dr. Capparelli.

DR. CAPPARELLI: Yes, I would echo one of the other requirements that we touched on earlier, that wasn't brought up: is that there is a significant amount of intra-patient variability. And so anything that's going to be assessing exposure really needs to be able to measure it well.

I echo, also, a lot of the comments about finding efficacy or effect from TDM in a controlled trial is very difficult. It would take a large number of individuals. And I don't think we're going to be able to implement a trial that's going

to show it conclusively. And so it gets into more of a religious argument.

[Laughter.]

But I think that even in the context of that shortcoming, there are going to be patients that will benefit from some monitoring of drug concentrations in the context of their clinical care, along with other information.

DR. ENGLUND: I would just like to add that in my experience, relatively limited, if there were a patient population it would be in the more highly treated patient with multiple problems starting out. I mean, if one were to focus the effort, that's where one would be focusing on it, because that would, in fact, help you with safety.

Any other comments?

DR. GRANT: I wanted to ask Dr. Gerber: if the point of this is really to minimize toxicity, shouldn't it be C_{max}s that they're looking at, rather than C_{min}s? Typically, with antibacterials, we look at C_{max} as the best index of toxicity.

DR. GERBER: Well, I think it varies from

drug to drug. It's unclear--for certain drugs it's clearly the C_{max} that causes toxicity. But for some drugs it's the overall exposure, AUC. So it's difficult to say.

C_{max} is impossible to measure. That's going to change from patient to patient, especially if it's taken with food, because food alters the gastric emptying, and that could be variable, depending on how much food you're taking.

So if you're looking at C_{max}, it might be difficult to design a study around that.

But C_{min} or, you know, C_{12}--something that can be looked at. But again, the accuracy of your timing of when you collect--as you mentioned--is so critical. And it's so wrong, frequently, that it makes it very difficult to do a study.

DR. ENGLUND: With that--Dr. Birnkrant?

DR. BIRNKRANT: We have a clarification here.

DR. GAGABUDU[ph]: This is Joe Gagabudu, Pharmacometrics, FDA.

I just have a quick--I would like to

clarify two points.

The first point that was made about the five points on the ALT elevation was the same in graph, all the 52--all the subjects from study 52 were used to get the line. The symbols only indicate the group averages at each interval.

So the curve is not derived just from five points. It is derived from all the subjects enrolled in the study.

The second point is: the relevance of C_{max} versus C_{min} is only an argument about--they're correlated. The only samples we had were C_{min}. But if you had C_{max}, they would have a perfect correlation between C_{min} and Cmax. So it's just the coefficient that is being different. But it does not matter, really, that we don't have C_{max}.

Thank you.

DR. ENGLUND: Okay.

With that, we're going to move on to Question No. 7, due to the time period.

DR. BIRNKRANT: I think the fact that we were moving so quickly recently, I think that we

can quickly just briefly discuss how you would like the resistance data displayed in labeling--be it for this drug or other drugs.

DR. ENGLUND: And we are fortunate to have some--

DR. BIRNKRANT: Some examples here that we can look at.

DR. BIRNKRANT: So our team looked at, or conducted a number of analyses based on baseline number of mutations, type, baseline phenotype, etcetera. The looked at various endpoints, with and without T-20 use.

[Slide.]

So in the next slide, one example of displaying the data includes the other active drug that was used in this trial--namely, T-20. And then you can see that we have the number of baseline mutations present in this table, and the data is presented at 24 weeks.

[Slide.]

In the next example, you can see a graphic display of data. And one of the key issues here is

that earlier time points are displayed.

So we'd like the Committee's feedback on the most informative way to display the resistance data from the trials.

DR. ENGLUND: Dr. Miller?

DR. MILLER: I think the graph actually shows more information that would be easier to understand for the people out there. The only problem is it doesn't include the n's, which the table does.

So if you could somehow include the n's without making it too complicated.

DR. ENGLUND: Dr. Munk?

DR. MUNK: Yes, my concern about both of these displays is that I think we've seen several times in recent years how a gross number of mutations gets overturned as we learn more about which mutations specifically affect the performance of the drug.

So I'd be leery of either one of these displays.

DR. BIRNKRANT: Are there any other

suggestions, then?

DR. ENGLUND: Dr. Miller? Dr. Grant, did you have an opinion?

DR. GRANT: Well, I think the graph is easier to look at. The other table is more difficult.

I guess I wanted to add, though, that it's not clear to me how the FDA list of mutations was derived. And it looked to me like it was less predictive than the tipranavir score that was developed by the manufacturer.

So I would not recommend using the FDA list of mutations unless it could be demonstrated to perform better than the tipranavir score.

DR. ENGLUND: Yes?

DR. DeGRUTTOLA: I think that this is one situation in which whether the table is used, or whether the graph is used--to get some sense, again, of how well you're able to classify individual patients; what proportion of patients that fall in one category--the more sensitive category--actually did get a good response, with

some measure of uncertainty; and what proportion that fell into the class not expected to do so well got an appropriate response.

And I think, just as was mentioned, to look at different ways of coming up with those classifications, including the FDA-identified mutations, and also the tipranavir score to see which one does the best at classification would be useful to do.

But I think the classification is important just to give a sense of what proportion of patients, even if they fall into the--quote--"good class" will still have problems is useful in a setting where there are toxicities of concern.

DR. ENGLUND: Dr. Miller?

DR. MILLER: I think I want to comment on the comment that Dr. Munk made, which I think is a good one. And this is going to be happening all the time with all the drugs, especially as new drugs get included. So if you have a PI that gets approved that causes a mutation that we haven't yet

seen, that's going to reconfigure this whole mix.

So I think what the FDA, what the agency really needs to do is to consider an ongoing review of baseline resistance and outcome as time progresses. But the information you have currently is what people need to know.

But this may not be current next year. So there needs to be a mechanism where the pertinent resistance information gets reviewed and the labels get updated.

DR. ENGLUND: Dr. Maldarelli?

DR. MALDARELLI: I think if you use the graph or the table it should be clear that the data were generated with a group of patients that were PI-experienced, but not the deepest salvage.

So I think people might see this and say, "Well, I have the most experienced patient, I might expect the same kind of response"--when, in fact, these data are restricted to patients who were enrolled with a specific set of resistance mutations.

DR. ENGLUND: Dr. Wood?

DR. WOOD: The one thing I like in terms of the display of the data: the table, I think, gives an immediate assessment of the proportion of

virologic responders, which I think is one of the primary focus of clinicians. I think the other thing about the table that's beneficial is that there's the clear demonstration in terms of the superior efficacy with the addition of T-20--which is not specific to T-20, but the fact that it represents an active drug.

And I think that you want to encourage clinicians strongly to really try and prescribe this drug with another active agent. Otherwise, you're not going to achieve the kind of virologic outcomes and, ultimately, durability and, hopefully, clinical benefit that you want.

So my preference would be for the table.

DR. BIRNKRANT: One additional comment.

DR. NAEGER: I just want to clarify that the FDA number--the 13 that we chose--is we're trying to remain consistent for all sponsors because we wanted labels to be more consistent.

If we had a different set of PI mutations for every drug--because every drug is going to have a different one--it becomes more complicated for physicians when they're looking at the label. So that's why we were trying to remain consistent.

DR. GRANT: But we--can I--

DR. ENGLUND: Yes.

DR. GRANT: I think you need to provide some guidance, of whatever information's available about what mutations actually predict response. And using a common set of mutations really obscures that fact that this now is a new PI, with a different pattern of resistance.

And so I think that using the tipranavir score, or at least including that somewhere in the label is really important to allow those groups that interpret genotypes to formulate rules based on the best possible algorithm.

And this is a PI with a different resistance pattern. So it's not clear that there's--in fact, there's not supposed to be a common set of mutations which apples to both this

drug and others.

DR. NAEGER: But the response that we're looking at of these patients are patients who have seen other PIs. So they're going to have this set of mutations. And then we're looking at whether these patients would best respond to tipranavir--not if they've seen tipranavir before.

So these are common mutations that are, you know, commonly in PI-experienced patients.

And using this number doesn't exclude us saying types of mutations that also affect response.

DR. ENGLUND: Dr. Munk, did you have another comment?

DR. MUNK: No, it's really the same one.

These may be common PI mutations, but they're not universal mutations. You can't say that somebody who's been on therapy with these three PIs, or any three PIs for five years in the aggregate is going to have the same list as others.

I agree, the situation is a lot more complicated than if you could have a standard list

of mutations, but I think that's reality. And I would expect it would be much more predictive of outcome to have a specific list of mutations.

DR. ENGLUND: Dr, DeGruttola?

DR. DeGRUTTOLA: I also remember that there were some mutations that tended to hypersensitive--if I'm not incorrect, 30 and 88--so, once again, calling into question the idea of using a common list when, in fact, some of the mutations might be beneficial.

DR. BIRNKRANT: Thank you.

DR. ENGLUND: With that--last question.

We are now are going to move on for discussion and recommendations of future study designs and data acquisitions for the heavily pre-treated population.

I think this is a ver important question, and one that I hope that we as a Committee can provide some input for, because we hope to be seeing more of these in the--some of us hope to see more of them in the relatively near future. And the distant future.

So, with that, let's be pretty specific in our suggestions and comments here.

Dr. Fish.

DR. FISH: One suggestion, in terms of data: the thing that I think would have very helpful for clinicians to have up front in this trial was, in real time, phenotypic data so that you can use the fold change when you've got a highly treatment-experienced population, and try and use that to your advantage when you're designing a cocktail.

So I think the phenotype does take a little bit longer to get, and it's going to delay your start of treatment. And that's a complicating factor. It would be helpful.

DR. ENGLUND: Would you say "in addition to genotype?"

DR. FISH: Yes. Yes.

I mean, certainly I understand for the trial design they needed the genotype to determine inclusion-exclusion criteria. But I think for these really tough folks, if you can get both, that

is probably the ideal.

DR. ENGLUND: Ms. Dee?

MS. DEE: Yes. I think--and people have said it--but I really do think that BI is to be commended for studying this patient population--probably the sickest patients we've seen in a lot of trials; and also to be commended for that 8-week escape clause, because there are plenty of physicians and patients who believe that, you know, these trials should be as ethical as possible.

Now, having said that, we're now stuck with this 24-week trial that is required under the accelerated approval regulations. And we have the agency using 8-week data to decide whether this is an efficacious drug or not.

So--where does that leave us, I wonder?

Let me see what I have written here, since I'm running out of gas.

So I saw a tortured analysis of what really is happening here. And I'm wondering what is reliable, given protocol violations and adherence

concerns.

And I'm also thinking about that salvage meeting that the community essentially tortured the agency until they had it, about trial design for salvage patients. And the reason that we did that was to get the word out that the agency was not opposed to the study of two investigational drugs in this population.

And unless we want to continue to sit here and wonder what really is going on in these trials--and I'm also thinking about--so, now the only plans that I saw in our packet here was to continue this same trial for 48 weeks. So what's that going to tell us if we don't know what's happening at 24 weeks?

And I'm also thinking: gee, I'm wonder if--you know, companies, "Well, it's so hard to get two companies together." And I bet Roche wished they had gotten together with you earlier, as far as getting a T-20 arm here. And I know we've convinced one other sponsor to look at two investigational drugs.

And unless other sponsors in the audience want to sit on these hotseats, I think they maybe need to get together with other companies. And the

only way to solve some of these problems is to do studies of two drugs at one time.

DR. ENGLUND: Perhaps we could just go around the table.

Dr. Wood? Do you have any comments? Or is this too early?

DR. WOOD: I would have to concur that there is the need to be able to--in this treatment population we clearly know that it doesn't need to be proven that adding a single active drug is not going to get you anywhere. You have to have a minimum of two active agents if you really want to see sustained kind of responses in virologic and immunologic surrogate markers. So I would have to echo the issue of promoting cooperation to study two investigational agents at the same time.

That is inherently fraught with a whole host of difficulties, when you're trying to then assess toxicity, and so forth, when you're dealing

with two investigational agents. But I do think that's necessary.

Again, as far as the heavily pre-treated population, I would just re-plead for the aggressive inclusion of women; the aggressive inclusion of individuals who are co-infected with hep C and hep B, because they tend to have more accelerated HIV disease, and there's really a need to be able to have a certain sense of assuredness in being able to provide new drug regimens in those heavily treatment-experienced populations.

DR. DeGRUTTOLA: Again, I think it would be very useful to have some clinical endpoints, even in these marker studies, both to try and get a sense of what the impact is of the randomization on the clinical endpoints; and also to try and relate the markers--the full suppression below 400; the less than durable virologic suppression, and the biologic non-response to some longer-term clinical outcome.

I also think that it would be useful to do analyses of the baseline mutations that predict not

only response and non-response but durability of response. And I agree with Dr. Wood about the need to recruit and understand better the impact of the drug in women and hepatitis-infected individuals.

DR. ENGLUND: Perhaps we could go on.

Dr. Rodriguez-Torres? Any--

DR. RODRIGUEZ-TORRES: Nothing to add.

DR. ENGLUND: Okay.

Dr. Munk?

DR. MUNK: Yes, I would just echo the comments that have already been made about including women, including co-infected patients with hepatitis, and especially the idea of studying more than one investigal--investigational--it's getting late--investigational agent at a time, because I'm thinking of highly experienced patients and how incredibly attractive that kind of a trial would be from them to enroll in.

DR. ENGLUND: My question to you is: could you then get a comparator arm?

DR. MUNK: Well, it's called a "matrix design." Ask that gentleman to your left. I'm

sure that there are ways to address the issues.

DR. ENGLUND: Dr. Gerber?

DR. GERBER: I have very little to add to what everybody else has said. I mean, I agree, essentially, with everything.

The only potential concern that I do have in these trials without a real comparator arm is if you have a drug that's more toxic than usual--if you had a safe drug that an efficacy--I don't think there could be any--you know, you could do whatever you want, essentially, and you would be able to demonstration, you know, virologic efficacy.

What concerns me is when you have a drug that's more toxic than the usual drugs that we use, is how do you evaluate how that drug is performing in the overall scheme of things?

And that's why I agree with Victor that we have to--you know, you don't want to have--we don't want to do a randomized trial and bring somebody into a state of opportunistic infection, but we want to be understanding how the toxicity of the drug is affecting the overall survival.

DR. ENGLUND: Dr. Grant?

DR. GRANT: I think we need to remember where this epidemic is. These studies need more

women, more Africans and more Asians. In these studies--in the RESIST studies--it looks like .7 percent Asians, and yet six million of those afflicted with HIV live on that continent.

DR. MILLER: So, basically, I agree with everything that's been said.

And, in terms of the study designs, we did have that meeting that Dr. Murray referred to, and that report was actually just published in AIDS, and a couple of designs are actually outlined in that paper--both describing how you could combine two or even three investigational new drugs, and also how to show the benefit of one new drug to the most benefit of patients.

So I think, you know, those trial designs did seem to make a lot of sense, and they came out of that meeting that was integrated; everybody that is involved in kind of thinking about these study designs.

One of the things--and this is something, probably, for a separate discussion--but I think it is time to start thinking about how the different mutations and viral fitness is going to start playing into all of this. Because some of the data was summarized here today and, you know, there's a

lot of data out there that even with multi-drug resistant virus, staying on treatment is beneficial, as compared to coming off of treatment.

And so I think some of those considerations. If we're going to be only focusing on the viral load response in these patients, and what that ultimate effect will be on the long-term progression, it may actually be useful to start thinking about how we might kind of bring CD4 cells back as more of a prominent marker than it's been--which is different than what you would do in the naive patient populations.

But, then again, I think--we keep talking about very heavily experienced patients, and I think we do also have to keep remembering that some of the patients will not be drug-experienced

themselves, but will have been infected by multi-drug resistant viruses.

DR. MALDARELLI: So, I think that the two points--I obviously agree with what we've all developed so far--but the design of the protocol as it was, using a rollover at eight weeks enable this trial to be nearly a placebo-controlled trial since so many people didn't even change their PI in the control arm, knowing that they could roll over later.

So that may not be such a bad thing. But it must be clear that we can identify the effect of the individual drug as it's being tested in an advanced population.

The second point which comes out of it is really managing the toxicities that we had. I think what we heard--and I think they should be investigated more aggressively than they were in this, and probably any of the other trials, as well. I think what I heard this afternoon was that everybody in front of me said, "What we need are better drugs," and everybody behind me said, "What

we need are better livers."

[Laughter.]

What we need is a better idea of what's going on when abnormalities arise. And maybe that means a better understanding of where those livers are at baseline; whether it's--and I'm not convinced that it may be a biopsy, but perhaps knowing whether or not people have fatty liver, either by ultrasound or some other technique that's not too difficult or invasive, may not be a bad idea to start with.

DR. MORSE: I switched from coffee to water. That was a mistake.

[Laughter.]

Two very quick comments. I think that particularly the comments directed at salvage patients is that I'm coming to think that maybe smaller numbers of more intensively studied patients may give us answers that will allow us to design better trials, rather than some of the current approaches that we've taken.

I think the approach of fixed doses for

everyone on a salvage regimen, when there's demonstrated pharmacokinetic variability, really almost demands that we try to investigate it and optimize drug exposure to whatever that susceptibility is in that patient. We'll never get to managing toxicity if we don't optimize the assessment of the antiviral activity.

The other minor point, I would say, is that there's been quite a bit of technology advances and, for example, in some of the studies where there are changes in area under the curve for a nucleoside, it's now very--not easy, but it can be done--where you include current measurement of intracellular triphosphates so you could then say, "Well, we don't know what 40 percent reduction means, but, no, we've got this data, and the 40 percent reduction was associated with this."

So I think there's enough technologic advances that may help out also.

DR. ENGLUND: Dr. Capparelli?

DR. CAPPARELLI: Yes, I wanted to echo a little bit about enriching the

population--especially in terms of racial makeup; in terms of ethnicity; and also in terms of pediatrics. And I'm very happy that Boehringer Ingelheim has taken that step, as well.

I also have worked in some projects from the pediatric standpoint where we have to be a bit opportunistic. And one aspect of the design which I do appreciate is we do have the control arm that we kind of lose a lot of information after they switch over. And that may be an opportunity for us to switch them over and do some of these other investigations, such as alternative dosing, in terms of how--drugs that we think we will want to use to manage some of the adverse effects, and doing some kinetic evaluation and some other evaluations in a more controlled environment.

So that intensity doesn't screw up your safety evaluation on your proposed dosing, but you get some information that's much more helpful to clinicians to manage these patients when they get to the outside.

DR. ENGLUND: Dr. Hall?

DR. HALL: Yes, I think it would be great in future studies to have a little more emphasis on the outliers--the people who don't seem to respond,

and the people who have the excess toxicity--to try and come up with sort of mechanisms as to why it's happening: are they getting low plasma concentrations for a reason? Do they have something in common? And vice-versa: are the high concentrations reflective of some underlying difference between the patients?

And I think in this context, and given the discussion about P-glycoprotein, then genotyping should definitely be a part of future studies to see if the expression of this transporter is in any way influencing both the plasma concentrations and then, of course, the lymphocyte concentrations, which may also be, in part, determined by the expression of these transporters.

So I think, looking out and being very inventive with regard to genotyping could pay off in identifying the extremes of the responses.

DR. ENGLUND: I would like to invite one

representative from the company--perhaps Dr. Mayers--just briefly. I think you have now a great deal of experience, from the company viewpoint, in this very difficult-to-study patient population. And we look forward to seeing more of this.

But could you give us any short viewpoint?

DR. MAYERS: I appreciate the opportunity to. We did learn a lot of lessons from this trial.

One of the lessons is: if I can ever do a placebo-controlled trial, I will do a placebo-controlled trial on this population, with another class of drugs. It makes life a lot easier.

I think one of the real problems that the Committee has brought up that we face is that: we can get outcome data. We've got 85 percent of the patients who were in the comparator arm rolled over. We actually have long-term vital status on 98 percent of these patients. So we know what their ultimate outcomes were.

But the problem is, it really becomes an eight-week immediate versus deferred tipranavir

study. So it's very hard to distinguish, if you're cynical, the difference between deferral tipranavir therapy and the potential that you have new toxicity because they've rolled onto your drug. And so how you distinguish bad things happening from when they're both on your drug becomes very challenging.

I think one of the things that the ACTG is doing that we'll probably integrate into our studies in the future is that when patients fail virologically and leave the study, we're going to ask them to stay in the study and follow them for safety data so that at least we can keep the balanced comparator for long-term studies.

Because right now, the 48-week data, as you can imagine, is actually more difficult to interpret than the 24-week data because you have 10 percent of patients who are doing marvelously who remain in the comparator arm--the 10 percent that got undetectable--and you have 50 percent of the patients in the tipranavir arm, half of whom are doing well, and half of whom are doing quite

poorly--but have nowhere else to go.

And so the comparisons get worse. They don't get better, in terms of trying to figure out safety from this type of a design.

And I think it's a real issue that's going to challenge all of us is: how you keep the trials with enough options for the patient that it's ethical, and you don't blow their last treatment option in the study but, at the same time collect enough data to give a meaningful interpretation of safety and efficacy.

I think the design we did did a pretty good job on getting efficacy. I think we have a good handle on how well the drug works.

I think it's not as good a design as we'd hoped for safety. And, as I said, one of the things we may well do is to leave people in follow-up who have failed treatment so that we can safety data. But the problem that then occurs is: if they all roll onto your drug, explaining the differences becomes challenging.

And I do want to assure the Committee that

we are doing everything possible to make the drug available for the back-up compounds other companies have. We've already combined it with several of the new non-nucs. We've combined it with--we are in plans of several of several of the CCR5 inhibitors--so that we're actively working with the companies to make the drug available.

The issue is, though, that all those drugs go through 3A4 and P-gp, and so you can't predict what the drug levels are going to be without doing the drug-interaction studies.

So we're currently working aggressively to get the drug interaction data in, to allow us to then move forward with them to include tipranavir in their pivotal studies once we know the drug interactions.

Thank you for giving me a chance to talk to the Committee.

DR. ENGLUND: Thank you.

Deb, do you have any other--

DR. BIRNKRANT: No other comments--just to thank everyone for their input. We greatly

appreciate it.

DR. ENGLUND: So--soon we get to leave.

I'm going to do a real short summary. I don't anyone to miss their flight because of it.

But I think we've had some very interesting discussion about future study designs.

One point I would like to add that--my two cents' worth is I think optimized strategy by an expert should be considered to be part of the comparator arm in the future; to make that mandatory, or something other than just "available if you feel like it"--because, in fact, sometimes that would be a little bit more uniform approach to the study.

So I think that's something for future studies, that that could be incorporated.

The recommendations for future study designs included many specific questions, such as real-time phenotyping; discussing what is a salvage design; and the fact that we, as a Committee, think that doing studies on at least two active agents at a time is going to be what is needed in the future.

For that, we need some creativity, cooperativity, and we need accessibility of multiple patient populations--including those who are infected HIV, which is women and minorities.

This is the same old story, and it's been said multiple times. We need to keep on and continue to emphasize it.

Rollover at eight weeks has been advocated by some in this committee to be an ethical and reasonable approach when you have not very many options. Toxicity management has been felt to be an important part of any new protocol.

And, finally, viral failure follow-up is something that needs to be followed up--emphasized both by the company and by individuals here.

So, with that, we're almost done.

The summary of this meeting I can't begin to do, but briefly-- we have discussed a lot of issues, including: study design; data entry; type of evaluation--including intent-to treat; patient populations; toxicity and safety; drug interactions; viral resistance--at length;

therapeutic drug monitoring.

And I think, importantly, we have an efficacy handle on this new therapeutic agent in the population for which it was studied. And I think we as a committee have agreed tat we feel that there is efficacy demonstrated. The exact usefulness of this drug needs to be monitored in the future, and we as clinicians need guidance--both from the company in future studies, and with the FDA--to be able to use this new drug in the best possible way.

With that, I will close the meeting. Thank you, everyone for coming. Appreciate everyone's input.

And congratulate the FDA and the company for their presentations today.

Thank you.

[Whereupon, at 4:58 p.m., the meeting was adjourned.]

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