have no real studies on hepatotoxicity on HIV medications at this point.

That's sorely needed. I don't see it being even really discussed very fervently.

DR. JOLSON: That's a fair point.

ACTING CHAIRMAN GULICK: Why don't we stop discussion at this point. We'll come back to these points. I would like to introduce our final speaker of the morning, Dr. Katherine Laessig from the Division of Antiviral Drug Products, to speak, to really summarize the public response and regulatory perspective.

THE STUDY OF ANTIRETROVIRAL AGENTS IN HEAVILY PRETREATED HIV INFECTED PATIENTS: A REGULATORY PERSPECTIVE

DR. LAESSIG: Good morning. The organization of my presentation is as outlined here. I would like to begin by defining some terms that are relevant to today's discussion.

Next I will summarize the responses we received to our request for public input regarding study components, including the patient population, study regimen, endpoints, and study duration, as well as review of specific study designs: historical controlled, open label, and blinded

intensification-type trials, concentration-controlled, and dose-response, and factorial.

Then I will elaborate on three potentially useful designs which were suggested. These include an add-on-type design, a two-part hybrid, and modified factorial. And, finally, I will end with some regulatory conclusions.

The heavily treatment-experienced therapy refers to a new or recycled drug regimen that is used to treat patients who have experienced therapeutic failure for either efficacy or safety reasons.

It is unlikely that a signal new drug will suffice as salvage therapy. However, for regulatory purposes, the contribution of a new drug to the regimen is what is of interest. This is in contrast to clinical management strategies, where the regimen is the entity of interest.

And, as previously defined for this meeting, the heavily treatment-experienced patients are those who have had previous therapy with more than or two HAART regimens containing greater than or equal to one agent from each of the currently approved drug classes.

I would like to differentiate between a drug of last resort versus one that might have a

broader use. This is a crucial distinction because it impacts the overall drug development plan.

A drug of last resort would have activity but might be restricted for use only in the heavily treatment-experienced because of toxicity, a less desirable route of administration, or other reasons. This is in contrast to a first-in-class or a next-in-class agent that could be used for both early or later treatment-experienced patients.

Now I will begin discussing the summary of the public responses. Regarding the patient population, aside from the definition we have already arrived at, it was felt that there should be broad representation of these patients, including those with low CD4 counts of less than 50 and high viral loads of greater than 100,000 copies.

In addition, aside from including patients who may have failed previous regimens due to resistance, patients who have failed due to pharmacokinetic tolerability or adherence reasons should also be included because they need new regimens as well.

Regarding stratification, which has historically been based on viral load and CD4 count, it is probably unnecessary for extensive

stratification because well-powered and randomized trials should control for the inherent heterogeneity, although examination of patient subsets may be useful for exploratory analyses.

Regarding study regimens, there was general agreement that resistance testing should be used to construct background regimens, expanded access agents should be allowed, and pharmacologic enhancers should be included. There should be flexibility in the number of background agents, and pharmacokinetic enhancers should not be included in the total number of background agents.

There is a caveat, certainly, that MegaHAART may decrease tolerability in adherence and increase overlapping toxicities, drug interactions, and number of dropouts.

Regarding the study duration, traditional approval has been based on demonstration of durability of virologic suppression to 48 weeks or longer, and there was no feeling that this should be changed. However, for accelerated approval, which has been based on 24-week data, there were suggestions that earlier assessment of antiviral effect should be considered for this population with longer-term safety.

So, therefore, I pose the question to the Committee that: When should we make the determination of an antiviral effect for these patients?

Regarding the endpoints, specifically virologic, proportion undetectable may not be a feasible endpoint except when using multiple investigational or highly potent agents.

Some alternatives which have been used in the past and may be appropriate in this setting include mean change from baseline and viral load, proportion with a greater than X log drop in viral load, area under the curve minus baseline. And we would gladly entertain any other suggestions.

With respect to non-virologic endpoints, specifically clinical, these have been previously new CDC Class C events, which equate to about 20 conditions.

Some suggested alternatives were to include fewer Class C events, specifically those that occur later in the disease process, such as CMV and MAC. Another possibility is a composite endpoint of efficacy and safety toxicity.

Our perspective is that there needs to be better collection and adjudication of clinical endpoints, regardless of the primary endpoint or the

patient population.

It is also difficult to weight toxicity in a composite endpoint. For example, how would one weight nausea versus CMV? And the agency needs to examine efficacy and safety separately to make risk-benefit assessments. Now I will move to a discussion of specific study designs.

There was general agreement regarding historical controlled trials such that historical results were not obtained in equivalent populations. This is due to the inherent heterogeneity and progressive heterogeneity of the heavily treatment-experienced patients.

In addition, there is an evolving standard of care. And one could argue that there is actually no consensus on how best to manage these patients.

In addition, there is probably incomplete data from historical cohorts to allow for adequate evaluation and comparisons, although the natural history of these patients on failing or currently available salvage therapy regimens is not disputed.

Our position regarding historical control is that when there is a concurrent control that is feasible, a single arm trial is not advocated. However, use of a concurrent observational cohort may

be possible.

With respect to blinded versus open label trials, there was general agreement that blinding all drugs in a study regimen is difficult due to a large pill burden, unavailability of placebo, and a consensus that resistance testing should be used to design optimized background regimens. Therefore, partial blinding of test and control is sufficient.

There are also multiple statistical considerations for open label studies, specifically that blinding reduces bias. And some of the source of the bias is that patients and physicians have expectations when treatment assignments are known.

There is a potential for differential dropout due to switches of treatment or loss to follow-up, which need to be accounted for in the analyses.

One method to assess the potential for differential dropout that has been used successfully is to monitor subsequent enrollment of patients in the clinical trials for a given investigational agent who discontinue that trial into that drug's expanded access programs.

Regarding intensification trials, which were defined as adding on a new agent to a preexisting

regimen with incomplete viral suppression, there were concerns on all sides that this may promote resistance because it is essentially mono therapy and it may exhaust an option that could have been used later.

However, it may be potentially useful if resistance to an agent develops slowly. In any event, the duration of intensification should be short and include an early escape option for suboptimal virologic response.

Regarding concentration-controlled dose-response trials, the community feedback was generally favorable because this avoids suboptimal levels. And higher drug levels may overcome resistant mutants.

There are multiple industry concerns, including that real-time reporting for dose adjustment in trials is difficult. There is high intra and inter-subject variability. And patient adherence may impact results.

In addition, it is unclear which specific exposure measurement is best correlated with response. There was also some feeling that the maximally tolerated dose should be used in this population.

Next. Regarding the dose-response trials, these have previously been used for registration of

antiretroviral agents. However, to discern a treatment effect is necessary to study doses on this deep part of a dose-response curve. Unfortunately, some participants may receive suboptimal doses.

We certainly agree that higher doses may be necessary to suppress resistant virus. Some of these points are illustrated by the following slide, which compares the dose-response curves of the wild-type, intermediately resistant, and a resistant virus to drug X. The *x*-axis shows log of the concentration of drug X, and the *y*-axis shows percent of virologic suppression.

For the wild-type and intermediately susceptible virus, dose one and two will show a treatment response because you are on the steep part of the curve. However, for the resistant virus, you won't see a treatment effect. It's not until you get to dose three that you will actually see a treatment effect.

The problem lies that we may not necessarily know how far to the right the dose-response curve has shifted for a resistant virus. This emphasizes the need for appropriate dose selection in the heavily treatment-experienced population.

Concentration-controlled trials have not to date been used for registrational purposes for antiretroviral agents. We agree at this time that there are assay considerations such that they are unapproved and not widely available, although this may change with time.

Regarding a true factorial design, the industry had concerns about the potential for drug interactions overlapping toxicities, the difficulty of ensuring a timely availability of drug supply, and the ultimate ownership of IND and data.

Although the community and FDA are in favor of this approach, the industry concerns are valid but certainly not insurmountable. The factorial design can be modified to be useful. And a factorial design is a randomized trial that participants are more likely to complete because they may be able to receive more than one investigational agent.

An additional benefit is that expenses for one trial can be shared by two or more companies. And since the company is already collaborating, blinding and provision of placebo should be easier.

Now I will discuss three suggestions of potentially useful trial designs. The first two are non-collaborative studies of single investigational

agents. The first is an add-on to optimized background regimen. The second is a so-called two-part hybrid. Then the third design is a modified factorial, which is a collaborative design for more than one investigational agent.

So the add-on is optimized background regimen plus or minus placebo versus optimized background regimen plus study drug. Randomization in blinding is preferred. However, this is a less desirable design that modified factorial due to the fact that some patients will be randomized to receive placebo and some will only receive one investigational agent. However, the risk of patients is lessened by having an early escape option for suboptimal and virologic response.

This is the second design, which is a so-called two-part hybrid design. It's designated two-part hybrid because for the first ten days, the patients are randomized to one of three arms. And the second part is a prospectively designed cohort, where all patients receive the same treatment.

The *x*-axis shows time and days out to day ten and then a break in the access in weeks out to week 24. The *y*-axis is log viral load.

Patients are randomized to one of three

arms: drug X plus their previous regimen, optimized background regimen, or their previous regimen alone.

Next slide. Since the trial is essentially uncontrolled after day ten, the contribution of the study drug to the treatment effect can be demonstrated by incorporating evaluation of an indirect dose-response through the use of prospectively defined phenotypic cohorts. In this example here, patients with more susceptible virus achieve a better virologic response, which provides evidence of the activity of the study drug.

So, again, the two-part refers to an initial randomization and then a prospectively defined observational cohort. In addition, it refers to the determination of the antiviral effect, which is directly assessed during the first ten days and then indirectly via correlation with baseline phenotype for the remainder of the trial.

Although the ten-day chosen for this example is just arbitrary, the assumption is that the lead-in period is brief enough so that patients on their preexisting regimen plus study drug X don't develop resistance to drug X during that period and patients continuing their preexisting regimens don't have adverse consequences due to not changing

therapies sooner.

Clearly the lead-in period needs to be long enough to assess an antiviral effect and to demonstrate that. This type of design probably would provide supportive evidence in an NDA package.

The third design is a modified factorial design; in this example, a four-arm trial for three investigational drugs, A, B, and C. Arm 1 is optimized background regimen plus A plus B. Arm 2 is optimized background regimen plus A plus C and so on.

The assumption is that optimized background regimen or optimized background regimen plus a single study drug alone is inferior. A major benefit of this type of design is at the end, it is 33 percent less than would be needed for three separate trials, this because the same active arm is compared against three control arms.

Now the unavoidable regulatory conclusions. The focus of today's meeting is drug-specific and not centered on regimens or management strategy. We need to determine what the contribution of a given drug is to safety and efficacy in broad patient populations as well as in the heavily treatment-experienced.

Some caveats about these trials is that we

need to know the drug interactions up front and that dose selection is very important and may be different for the heavily treatment-experienced. In addition, the baseline resistance testing is useful for construction of the optimized background regimens and also for outcome analysis.

Some additional points to consider are that multiple agents make determination of adverse event causality for drug toxicity difficult. Trials of shorter duration may adversely affect the safety database.

Resistance may develop to first-in-class agents and compromise later virologic response to next-in-class agents. Therefore, we need to provide data for a spectrum of patients, particularly the heavily treatment-experienced or first-in-class or promising next-in-class drugs.

It is important to consider the overall strength of an NDA package. One controlled study plus other well-designed studies in the heavily treatment-experienced may be preferable to two identical studies and naive in less treatment-experienced patients.

Lastly, all study designs must take into account targeted use of the drug, heavily

treatment-experienced versus all patients.

Now I will turn it back over to Dr. Gulick.

ACTING CHAIRMAN GULICK: Thank you.

Are there clarifying question for Dr. Laessig before we launch into our discussion? Ms. Dee?

MS. DEE: Just one comment. You know, in that Slide Number 3 about the three investigational drugs, for instance, we could use Kaletra as one of those drugs. Even though it is approved, there are a lot of patients who haven't yet had the opportunity to use this drug. So this is not always dependent on three investigational drugs per se.

QUESTIONS TO THE COMMITTEE

ACTING CHAIRMAN GULICK: Okay. Thanks.

The way I think we should approach our discussion is to recognize a couple of things. We are going to do the discussion actually in two parts: one prior to lunch and then one after a few presentations in the open public hearing after lunch. So we will probably get through some of the questions but not all prior to lunch.

Secondly, just note from the questions that the questions for the morning really are trial

design issues. And then we're going to make a switch after the open public hearing to endpoint issues. And it would be helpful to try to leave the endpoint issues for the afternoon after some formal presentations.

The last request I have is that Dr. Laessig outlined three potential study designs that we will discuss as a group and others around the table have other study designs they will present.

I think before we jump into specifics, it is appropriate to address Question Number 1 first before we get into the specifics of the individual studies. And here we have it.

So the question before the Committee, the most broad question, about treatment in heavily experienced patients is: What type of information would you most like to see from studies conducted in treatment-experienced patients, both adults and children?

And then, as a general question, more specifically comment on the use of studies in these populations to support the efficacy for registration versus their use for supportive information for addressing more focused questions, such as drug interactions, dosing, and resistance issues.

So who would like to start us off? Dr. Saag?

DR. SAAG: I think that, even though the meeting has defined what the treatment population is; that is, at least two HAART regimens in all classes, still begs the question of those highly experienced patients who have really gone through all options because I sense that there is some confusion about what optimized based background therapy is.

For example, optimized background therapy is more likely to work somebody failing their second HAART regimen versus their eighth HAART regimen. I think that has to be taken into consideration when we talk about designs later.

The bottom line I think we need to talk about is: What are the objectives of treatment, just in the clinical situation and then about it from a trial situation?

At least in our clinic, it's a lot different maybe than Dr. Ward's. We're having a lot more treatment failures than he presented. We're having at least a death a week now back again. So we have actually more than that. We have 70 deaths this year out of our 1,000 patient population, which is maybe different than what other people are seeing.

Perhaps that's because we were using protease inhibitors early, early on, but whatever the case is, it's what we're seeing.

In our situation, what we are finding is that we are having to redefine what our goals of therapy are for those patients. So that's what I want to present as a point.

In those patients who have really, really far advanced in multiple HAART regimens, we were far away from the cure paradigm. So, therefore, treating to the level of detection is not even discussed. It's not what we're going for.

Rather, what we shoot for is some decrease in viral load below their highest set point value that we can define. Usually that is easy to get because they have had a holiday somewhere along the line where they have bounced back up to, let's say, 400,000. And then we're happy just to get them a .5 log below where they started.

I think that in that scenario, what we're really doing here is -- I am not really as concerned about prevention of resistance. They have already got that. What I am concerned with is prevention of clinical progression.

I think that in my sense of coming to this

meeting, when I'm thinking about a salvage situation, that's the population that I'm thinking of.

So preventing resistance is a secondary or tertiary objective at this point. The goal is to keep people alive and living well. In that regard, I would propose that what we ought to think about is getting patients to at least a .5 log below where their highest viral load has been and sustaining that for as long as we can. And whatever drugs or strategies accomplish that I think is a key point.

So what type of information would I like to see from studies? I would like to see regimens in this salvage population, the highly advanced treatment-experienced patients, to sustain at least a .5-log reduction in viral load from their baseline and sustain that for as long as possible.

ACTING CHAIRMAN GULICK: Dr. Deeks?

DR. DEEKS: I entirely agree with basically everything that Mike just said. I would like to add onto that and speak to some of the comments that Dr. Schechter had made earlier regarding the heterogeneity of our patient population.

I think as the way we define the heavily treatment-experienced patient population right now, it's very heterogeneous. I have patients who have

failed 3 classes of drugs who have 500 t-cells, a viral load of 5,000, and are doing very well.

So across all patients, there is a huge amount of heterogeneity in this group of patients, but I do believe that this patient population is ultimately moving toward less heterogeneity.

And we have and Mike does as well, I think, a small group but a growing number of patients who have very high viral loads, very low CD4 t-cell counts, an RT protease genetic background that is inconsistent with any real good antiviral response to any drugs now.

I would agree with Mike that these patients are now getting very sick. We have actually a large number of deaths in our clinic as well, and many of these patients are now dying from clear HIV-related complications.

So when I think of salvage therapy, I have a very different mind set. Like Mike does, I'm thinking now of that group of patients who have ten t-cells and who have run out of options for whom a study that was a single arm and had only one drug; for example, T-20, would be something that would be highly desirable to me, something that my patients would be very much interested in going into.

And I would prefer to have access to those studies for that patient population, in contrast to the A plus B versus B plus C-type stuff, which I think is more designed for patients who are less desperate earlier on who might be able to wait for that type of study.

So, actually, the bottom line is I think that there is less heterogeneity in this very, very heavily treated patient population than some of the presentations which exist.

ACTING CHAIRMAN GULICK: Dr. Schapiro?

DR. SCHAPIRO: First of all, since this deals with resistance assays, I would like to add to my disclosure that I received financial support from Visible Genetics and research support from ViroLogic, both that deal with resistance assays.

I think, to touch on the points that Mike and Steve mentioned, we mentioned drug, but I think we should realize that the way we use drugs makes them different drugs.

We categorize a drug based on a certain approval on the studies that were done, but I think we should realize, I think a lot of the work done by the previous speakers, shows us that the drugs are really different drugs when you use them at different doses

at different schedules.

And although we may say this patient now has no options, we're really looking at the data on the way the drug was used in naive patients. And we should keep that in mind.

When we try to compare, you know, we stratify for resistance to this drug, resistance is relative. It's completely relative. Drugs are not resistant or susceptible. They become more and more resistant or less and less susceptible as mutations or full change phenotypic resistance occurs.

So we probably have to add for dimension drugs are not black and white. We probably have to consider the dosing of the drugs. I think we have the most data for protease inhibitors, but we might find as we learn more about the other drugs that in other classes of drugs, we may have ways of boosting them as well.

There may be metabolic ways of boosting NRTIs, which are around the corner. But definitely for protease inhibitors, if we consider how we are using them in the salvage patient, we may actually find that the same drug is a different drug when we use it in naive patients, where we will look for considerations of easy adherence, minimal toxicity.

And when we have the patients, I think that Mr. Hogan described earlier that Steven and Mike touched on patients that in clinics are dying now again.

For those patients who will look at the drug entirely differently, we'll be willing to administer the drug more frequently and possibly much more toxic doses.

We're really not going to get all beat up about some metabolic changes if the patient isn't dying. And I think when we make this discussion, we should consider the fact that the drugs are relative. We cannot put down how many mutations affect this drug without considering what exposure the drug is getting.

Therefore, I think in some of these study designs, we should keep in consideration that we have to be looking all the time not only at resistance but at exposure. And we cannot make sweeping conclusions about drugs and resistance but how we are going to use them.

And since basically these patients don't have options, we have to be creative. We're saying, "Oh, these are patients who have no options. So how are we going to optimize therapy if they have no options?" There is no optimizing therapy. We have to

take into consideration that we may have to be creative.

I think what it will probably mean is using different doses, and we will have sort of a sliding degree of toxicity and no exposure.

ACTING CHAIRMAN GULICK: Dr. Pettinelli?

DR. PETTINELLI: What I would like to see in this patient population is a comprehensive approach. I think that there is space for registrational trials. There is also the possibility for other trials.

I totally agree with Mike and Steve. This patient population is very heterogeneous. In the one, there is maybe a possibility for some of them to build up to what we call an optimized regimen on the base of the resistance, phenotypic resistance assay, genotypic or phenotypic resistant assay. If we can do that, then we could indeed do some of the trial that has been proposed in our standardized optimal therapy versus one or two new drugs.

For others, that will not be possible. I hope that during today we will discuss the different possibilities for these different patient populations.

Also, I think what I would like to see, really, to understand what is the long-term efficacy

of whatever intervention we do, one may be that 24 weeks is enough for accelerated approval. I don't think it is really enough to understand how we are going to use these drugs.

So definitely we should have a longer-term follow-up. And then, additionally, we really should understand what happens when those patients are failing. Now we're talking in certain standards the earlier failure. When those patients fail those regimens, what are the options afterwards? We might have a drug that's very powerful but then limited successful options.

Those are things I think we should discuss today.

ACTING CHAIRMAN GULICK: Could people comment on testing the activity of a new agent in this patient population? In other words, what are you looking for? And what kind of duration would you call for to demonstrate that activity?

Currently -- correct me if I am wrong, but regulatory-wise 24 weeks of activity data is what you like to see for an accelerated approval. Is that different in this patient population? Dr. Eron?

DR. ERON: Well, I think there are a couple of issues. I mean, I agree with both Mike and

Steve and having clinic populations that are probably similar. But where it gets dicey is: At what cutoff of, for example, CD4 cell count do you consider a patient unable to wait for a combination of agents? And that's something that I think would take some discussion to limit the heterogeneity of that group as much as possible, though I think it can be done.

I think what you were suggesting was a single arm study. I actually think that if you can define the group well enough -- and I think there are enough patients now that you can.

I think, to try to get to Trip's question, for other than that kind of single arm study, I think what is different in the salvage setting is the amount that is kind of Phase II work that one has to do before approaching a larger Phase III trial when you talk about what happens at 24 weeks or whatever.

I think in the population that you're going to test, you want to define the activity of the drug because there may be two logs over two weeks in naive patients, but it may be half a log over two weeks in the population you're after. And in order to design a study, you need that type of information. I think that's a little bit of what Jonathan was saying, depending on the background resistance.

So before you embark on figuring out whether it is 16 or 24 weeks, I think the drugs, each of them, need to be defined very carefully. And, in addition, we have lots of examples of kind of these whoops examples, where "Whoops. We didn't know about that PK interaction of efavirenz and amprenavir." I think we have to minimize those kinds of things.

So while the second part of the question deals with what I am talking about, I think those are things that have to be carefully defined first in order to address the first part of the question.

As far as duration in a larger trial, I think, again, Steve is probably as equipped as anybody to talk about that in the issue of transient viral load changes accompanied with positive CD4 responses.

One of the earlier speakers mentioned no viral load change in a positive CD4 response. I've not really seen that before. There is always some change, even though it's transient.

So I think that for the purposes of taking care of very advanced patients, the amount of time that the antiviral effect has to last does not have to be very long, 8 weeks, 16 weeks, something like that, provided it's accompanied by an immunologic benefit. So I think you would actually want the immunologic

change to be actually part of your primary evaluation.

ACTING CHAIRMAN GULICK: Dr. Jolson?

DR. JOLSON: I just wanted to slightly rephrase this first question to make certain that we really stay focused. Again, it's recalling the distinction between trials that are done in the course of drug development for a specific drug versus treatment strategy studies.

What we would really like to hear your thoughts on are the former, the studies that could be done which would allow a sponsor to make a specific other efficacy or safety claim about their drug when used with other drugs. It's probably unlikely that is going to be accomplished through a single orb study unless there is an appropriate historical control group or there's some other indirect analysis incorporated into the design.

It's not to minimize the importance of those strategy trials, but it's a slightly different research agenda than what pharmaceutical companies need to make lawful claims about their drugs.

So I would reword the question to say, "What types of information should be in drug-specific labeling that would help it when making treatment decisions to use a particular drug in

treatment-experienced adults and children?"

ACTING CHAIRMAN GULICK: So you're asking us to consider: How do you document safety and efficacy of a new drug in this patient population, a single new drug?

DR. JOLSON: Yes or safety and efficacy in a broad way, which would include drug interactions and all of those things, how you develop a drug, develop a new drug, to make certain that at the end of the day, you don't have all of your data derived from treatment-naive patients.

ACTING CHAIRMAN GULICK: Dr. Saag?

DR. SAAG: Yes. Just to follow up and answer the question directly, I don't think you need necessarily a single arm study, but you can look at early versus deferred access to that new agent.

I mean, I'm being very specific. The population whom you're questioning, as Carlton was saying, whether even to treat them at all, whether it's any benefit to the control therapy, then what you do is you take them, you create an optimized background regimen, and you randomize, indeed, or get access to the new drug or the optimized background regimen initially and then you watch for a response. I mean, we can debate about what the cutoff is, but

let's say a half a log below baseline.

Then for the group who got their optimized background regimen and did not have that response, that would be failure. And it would go into access to the drug, which is like an expanded access program anyway.

If they did have a response, then you measure the length of response. You also measure the safety. You get safety out of both populations, and it's early versus deferred.

Again, we have to be very precise about who is going into this study. It's a study of someone who has very few other options and is at risk of bad things happening in the short term.

It's I think ethical because they get access to the drug. It's just a question of careful monitoring and making sure you, if you will, rescue them from a failing regimen if they are failing quickly. So it requires frequent evaluation so you don't put them at high jeopardy.

ACTING CHAIRMAN GULICK: Dr. Wong?

DR. WONG: I think that what Mike suggested is really quite a good design. I mean, we yesterday, just yesterday, voted unanimously to recommend approval of a drug for which there were no

concurrent controls and for which the only controls were a flawed historical subset.

So this design that you're proposing is superior to that. I think that would convince me if someone came in and showed data that there was a clear difference between those groups.

ACTING CHAIRMAN GULICK: And another common thread, just to point out, between yesterday's discussion and today's, is a very ill patient population who have few therapeutic options. That's what they have in common.

Dr. Murray?

DR. MURRAY: I just wanted to comment on one of the comments I guess from Dr. Deeks and maybe came up from Jules about maybe not preferring a factorial design in even doing a one drug versus a top of optimized background versus optimized background.

I guess I am not quite clear on that because, I mean, if you could possibly have access to two or three drugs, no matter how desperate, I think that even if you were more desperate, if your t-cell count was low, that you would want access to more drugs than just one.

And I think this is something that we have been pushing and I think we would like to hear more

feedback to push industry to collaborate together. It seems like I've heard a bit of the opposite why you would -- is there any reason not to want a possible factorial design where you get access to more drugs for these patients?

ACTING CHAIRMAN GULICK: Dr. Mellors?

DR. MELLORS: Would it be too much to show an overhead about the factorial design and its major limitation?

ACTING CHAIRMAN GULICK: Knock yourself out.

MR. LEVIN: Are we talking now about studies for deep salvage or just treatment studies past the first-line regimen?

DR. JOLSON: The intent was really not to limit the discussion to what you're saying is deep salvage because we think there is really a range of patients who do need options and we want to see drugs developed across that range.

So this would be part of the discussion but hopefully will not be all of the discussion because the considerations are going to be different. And I think both groups of patients need attention in terms of drug development.

ACTING CHAIRMAN GULICK: While we're

waiting for that to warm up, a couple of other people. Dr. Cunningham?

DR. CUNNINGHAM: I just wanted to make a comment about the issue of factorial design. I think when people are talking about what people have now termed the "deep salvage" patients, I think that's a group where the factorial design might not be the best approach because those patients really need to have every option available.

But I think for the people to have "time to cruise," I think was the term that was used in one of the earlier talks, they certainly have failed one or two regimens, but they're not desperate. That's a situation where I think factorial designs might be very useful and might also look at the issue of whether or not you're better off cruising for a little while before you go into and wait until there are multiple regimens available and can test that hypothesis.

ACTING CHAIRMAN GULICK: Dr. Mellors?

DR. MELLORS: Yes. I think these points have been made, but I think they need to be emphasized. For a desperate patient population, a factorial design for registrational study is a bad idea because if you look at the way it's set up, --

and Martin pointed this out -- the number of cells required is 2^n, *n* being the number of drugs you're studying.

So if you study 2 new drugs, it's 4; 3 new drugs, it's 8; and 4 new drugs, it's 16. The number of cells that get all of the new drugs is one to 4; one to 8, one out of 8; and one out of 16.

So if you study 4 new investigational agents together, in a desperate population, only one-sixteenth of the people enrolled get what you would like to do in clinic, which is give them as many new drugs as possible. Okay.

And that's just shown here nicely for the two by two, where this is the cell you want to be in, two news. You really don't want to be in three news. You don't really want to be in this and this. And by "desperate," I would define desperate by the CD4 count because that is the most important predictor next to viral load of short-term events. These arms are probably less satisfactory than the nothing arm because they use up one option at a time.

So I don't think factorial design accomplishes what we want to do for our patients. It may tease out the individual components, but I think that's more efficiently done in the standard approach

that's been offered for registrational trial, which is you identify a qualifying population, you do resistance testing to see if they qualify, and then with that resistance testing, you optimize the background therapy. And I have some comments about what that means. And then you randomize to optimize background plus the investigational agent plus placebo.

By optimized background therapy, I think there needs to be some kind of guidance. You need to calculate the phenotypic or genotypic sensitivity score of the selected regimen and possibly stratify enrollment by the PSS or GSS and clearly allowed expanded access agents, have endpoints that are most clinically relevant, change in viral load, change in CD4, and the proportion that develop resistance to the investigational agent.

Then when you cross this over, it addresses the issue of safety. There's always a tension between the time of or the duration of the trial and the accuracy of the safety information.

I just have one more to show, and I think this is what Mike was talking about. I favor the design that a registrational trial should be comparing one new investigational agent to really optimize

background. That way it's easiest to sort out the information you want to know about safety, pharmacokinetics, drug interactions, and the relationship between exposure to response and the relationship between exposure baseline susceptibility and response. When you start to do that in an eight-cell factorial design, it becomes much more complicated.

The strategy trials, which should complement the registrational trials, are to compare multi-drug regimens that increase the likelihood of success. And this is what Mike was talking about, taking the most desperate population and comparing multiple drug regimens with new investigational agents versus the best approved or expanded access regimen that a clinical can put together. These should be relatively short with crossover at an arbitrary time but closer to 16 weeks than 48 and/or a clinical event and CD4 and RNA response.

So I think that the strategy should satisfy our need to treat patients with the most available expanded access or investigational agents. The registrational trial I think has a hopeless problem when you want to treat the most with the most number of investigational agents.

ACTING CHAIRMAN GULICK: Dr. DeMasi and then Mr. Hogan.

DR. DeMASI: Yes. I just had a couple of general comments. First, I wanted to reinforce John's comments about the factorial design. Obviously one of the advantages of factorial design is being able to get multiple investigational agents to patients in a particular study but in a balanced two-by-two factorial, as John just pointed out, the number of patients or percentage of patients that have access to both investigational agents is 25 percent.

If you do allow the use of investigational agents as concomitant to antiretroviral medications as part of the optimized background regimen and you add a component, such as a two-to-one randomization, to the investigational agent of interest, if two-thirds of the patients are on that agent and because of the patient population approximately 50 percent of the patients have access to the other agent, 35 percent of the patients have access to 2 agents. Therefore, it's actually higher than what you would have in the two-by-two factorial design.

So the combination of a two-to-one randomization and the use of investigational agents I think is a way to promote optimal use of

investigational agents in a single study.

The second point I wanted to make is just one of the distinctions between the efficacy of the regimen and the activity of the individual drug. If you look at multiple drugs that have intrinsic antiviral activity, as measured by 10 to 14-day responses, for example, in RNA, and you combine those in a multi-drug salvage regimen, you are most likely going to get efficacy of the regimen beyond 2 weeks.

That's something that could be confirmed but just to reinforce the distinction between the efficacy of a salvage regimen versus the activity of an individual drug that is being studied for potential approval, submission and approval.

The third point I wanted to make is regarding the types of the clinical designs, clinical trial designs, that we're actually seeing. Because of the heterogeneity of patient population in terms of the baseline factors resistance profile, I think that a one-size-fits-all strategy in terms of development of salvage drugs may not be appropriate and that there should be flexibility in the design of pivotal registrational trials in terms of selection of the patient population, the design itself, the duration of therapy, and other factors.

ACTING CHAIRMAN GULICK: Mr. Hogan?

MR. HOGAN: I would like to politely but very strongly disagree with Dr. Mellors that the desirable thing is to pile on as many new drugs as possible. I think I can speak with some authority to this issue because it was prior to the era of HIV RNA testing, but I have experienced facing a single t-cell. You know, it's a very serious clinical situation. So I think I can extrapolate how I would feel in that situation.

I had always been on combination therapy from the days of ddI expanded access. Yet, I had no desire to pile on more drugs at that time.

I think, particularly with experimental drugs, you have some credible dilemmas if you pile them on all at once without some form of comparison between them.

For example, if I pile on three investigational agents and I have a novel toxicity, which one do I stop? How do I determine which one to --

DR. MELLORS: Can I respond to that?

ACTING CHAIRMAN GULICK: Yes.

DR. MELLORS: You determine that in a registrational study design that I outlined. The

individual characteristic of that drug is the cleanest way to do it. You then design strategy trials that incorporate the information from that into multi-drug combinations.

I would agree with you you don't blindly pile on investigational agents. I'm talking about agents that have proven activity and a reasonable safety profile when examined in addition to background therapy.

MR. HOGAN: I guess a key point is as a patient, my preference would be to take the minimum number of drugs that will achieve a satisfactory response. And I would like to see clinical trial designs that would establish that.

So that's one reason why I'm a fan of the factorial approach because it does allow you to look at the individual toxicities of drugs, to look at specific subcombinations, AB versus BC and so forth, and then it allows me to find out where I can get adequate antiviral bang without excess toxicity.

DR. MELLORS: We are talking about the people that are most desperate.

MR. HOGAN: I understand.

DR. MELLORS: And if you undershoot and come up with one drug too light in the regimen, that

may be it for that individual.

MR. HOGAN: Yes. Cardiovascular disease kills people as quickly as CMV.

DR. ERON: But, John, that I think is the fundamental problem of your study design for registration, actually. Just take a concrete example of T-20 and tenofavir. Let's say tenofavir is an expanded access in a couple of months.

The problem with your study design -- I think it goes to what Dr. Murray was saying -- is that if you're allowing expanded access agents in your control arm, then those people are getting exactly what you said you don't want them to have.

So if there is only one agent available which is going to prove anything, the optimized therapy really is just kind of scrambling around things. And you don't really know whether they're better or not.

DR. MELLORS: What's wrong with including the expanded access? By the time agents get to expanded access, the characteristics of the drug are fairly well-identified.

DR. ERON: No, but the point is that the people who get randomized to get the only one additional drug -- let's say in the expanded access

situation -- are ending up exactly in the situation you just said you wouldn't want someone to be in.

DR. MELLORS: There's an insolvable dilemma between the two.

DR. ERON: Well, we have to try to solve it. The potential might be for an optimized background or no change in therapy, as Mike was talking about, and sequential addition in very short order.

DR. SAAG: I would like to get out of this circle here because I don't think there's a lot of disagreement, actually. If we segregate out what's for registrational purposes versus what's for use in practice -- and they are two different issues. I don't think there's much disagreement here.

I think for the registrational purposes, you have to identify the activity of the drug because you can't approve it based on its activity in conjunction with other investigational drugs alone. You've got to have that individual.

I think that is what John proposed first. I think that still has to happen. What happens after that, maybe we shouldn't spend much time on because I think that that is going to bog us down.

MR. HOGAN: Well, here's I think a point

of key disagreement.

ACTING CHAIRMAN GULICK: Let's take people in order. Go ahead.

MR. HOGAN: I don't think it's reasonable to say that by the time we get ready for these studies, that the activity and tolerability of the drugs is necessarily well-characterized. And, again, I would refer you to the multitude of toxicities that have propped up post-registration for various drugs.

DR. SAAG: I'm not disagreeing. All I'm saying is that fundamentally, no matter how we slice it, there is going to be a need to identify the new drug and its activity and its safety.

We have to have some way of doing it. That's a given. What happens after that, you're right. Those can be happening concurrently. And you want to have as much early information as you can with the intent for that to happen. But I think from the company's perspective, from the agency's perspective, there has got to be some way to tease out the activity and safety of a single drug. And that's what we really I think should focus on.

ACTING CHAIRMAN GULICK: Dr. Hammerstrom?

DR. HAMMERSTROM: Well, I would like to say that Dr. Mellors is basically 100 percent wrong in

the relative merits of the 2 registrational trials versus a modified factorial design.

In his proposal, 50 percent of the subjects get on the control arm, either against drug A or against drug B. The other 50 percent get only one active arm. In the modified control, factorial design, where there isn't any optimum background cell, you add both drugs or you add one drug, nobody gets no new drugs. And everybody gets at least one. More than a third get two new drugs because the optimal assignment just on statistical grounds is 14 to the double thing, to each 10 on either A or B.

So you either have nobody would be getting -- in the modified factorial, nobody gets background. There are ten subjects who get A only. For every ten subjects who get B only, for every 14 who get A plus B, factor --

DR. ERON: The problem is it may be worse to get A only or B only than --

DR. HAMMERSTROM: But if you do a registrational trial, everybody gets background or background plus A or background or background plus B. Nobody gets A plus B unless you do a modified factorial.

ACTING CHAIRMAN GULICK: Dr. Schechter?

DR. SCHECHTER: Yes. I just want to echo that that, first of all, the bar has been changed. I think when we go into deep salvage, you're starting to move towards a tuberculous meningitis model, where the stakes are different.

I agree a single new drug tested in that population is entirely appropriate, especially if they're at such great risk that a second drug won't be available during this crisis period. So there's no disagreement there.

Simply put, if two companies are about to do registrational trials for drug A and drug B separately, then with the same number of patients from each company, they can do AB and AB and have two registrational trials and both drugs given for the same amount of money.

So I have to disagree with John. If he says only one-quarter of patients get the double therapy, if you do it separately, nobody gets it.

ACTING CHAIRMAN GULICK: Dr. Mellors, response?

DR. MELLORS: Yes. I think that the three cells that don't get the double --

DR. HAMMERSTROM: There aren't three cells. There are only two. There is no EBT cell.

DR. MELLORS: You're talking about a different design. I'm talking about a --

DR. HAMMERSTROM: No one wants the factorial.

DR. MELLORS: Okay. While I made that --

DR. HAMMERSTROM: They only want the modified factorial.

DR. MELLORS: I made the point that nobody wants the straight factorial design. The modified factorial increases the number that get the double drug. And if there are two companies that want to do a registrational trial together, then I'm certainly not going to stand in the way.

But knowing we're talking about a desperate population, two investigational agents may not be sufficient. So we're talking about a third factor in the factorial. There's where it becomes much more --

DR. HAMMERSTROM: No, it doesn't, because, again, we use the modified factorial, which Dr. Laessig's slide put up there. You have A plus B, A plus C, B plus C, or you have all three. Those are the only four cells.

DR. MELLORS: But you're not able to tease out the --

DR. HAMMERSTROM: I am certainly able to tease out each contribution. I test the three A, B, C against BC. That's the contribution of A. I test the A, B, C against AC. That's the contribution of B. I test the A, B, C against BC. That's the contribution of A.

PARTICIPANT: That assumes there is no drug interaction.

ACTING CHAIRMAN GULICK: Let's take the people in order.

DR. DEEKS: One of the issues --

ACTING CHAIRMAN GULICK: Okay. One second. Several people have been waiting patiently. Ms. Dee and then Dr. Deeks. Then we'll pick up some of the others.

MS. DEE: Thank you. You know, I think we need to get a little bit real here. When you talk to companies about registrational trials versus strategic trials, they're not going to do the strategic trials if they don't have to. Some of them might. Most of them won't.

So what do we have? If we use Dr. Mellors' model, we have this everybody's switching around, getting expanded access drugs maybe, maybe not. I really wonder what we're going to know when we

get down that trial in the long run.

We're looking at viral load measures that may be a measure of clinical benefit. Maybe they're predictive. And probably they're not as good as some other things.

As far as safety, you know, Mike keeps saying: Well, we need to know safety. And we'll know it in 8 weeks or 16 weeks or 24 weeks. That's just not true.

What we are experiencing in real life is one drug being ready, one drug being almost ready. I mean, we see this in real life over and over and over again. Why can't we do it together?

Carlton with one CD4, when is he going to get sick? What does "desperate" mean, that I just finished an OI, that maybe I'll get one in six months, that maybe I won't? I mean, we do not know the answers to how that really shakes out.

So we have a more intelligent population that often says: Well, wait a minute. I've been ruined re: resistance by you experimenting on me. If these two drugs are available and I may have a better chance in 20 hours, as opposed to 20 minutes. Why can't I have two of them? Why can't I have a better chance?

Why can't we think outside the box for a change, instead of promoting what's going to be best for industry, without thinking of the long-term effects of that?

ACTING CHAIRMAN GULICK: Dr. Deeks and Dr. DeMasi.

DR. DEEKS: I just want to answer Jeff's question earlier about the factorial design and my problems with that. My problems are that I just don't see it happening. There are major practical limitations.

I have dealt with each of these companies in trying to do similar types of studies before. I think it can happen. I just think it's going to take a long time to get three companies with three promising drugs to come together to do an A plus B versus B plus C versus the three-drug combination. The more likely factorial design looks at no drug versus one of the two agents versus both.

For my patients who are not desperate and can basically continue to cruise on whatever they're doing, I would prefer to cruise than to enroll them in a trial where they might get sequentially mono therapy.

For my other patient population who are

desperate, I would definitely want to enroll them in such a factorial design if they had an option of getting one drug, but, again, it's the practical issues that I think will slow down that study.

My preference for the desperate patient population, CD4 counts less than 50, is for the companies with promising agents to move very quickly to the kind of study that Mike had discussed earlier, which is basically optimize your background therapy plus the new agent versus optimized background therapy with a very quick escape.

My preference for that study design in the very desperate population is really largely based on the fact that such a study can be done very quickly and is much more practical than these --

DR. HAMMERSTROM: The factorial design doesn't preclude a quick escape. I mean, in fact, we would assume that. If you're on background plus A and things go wrong, you get switched to open label background plus A plus B.

ACTING CHAIRMAN GULICK: Dr. DeMasi?

DR. HAMMERSTROM: It would be the same switch criterion as if you were only doing one trial. There would be no problem with that.

DR. MELLORS: But that presupposes that

you can switch in time to make a difference. And that is a major supposition.

DR. HAMMERSTROM: That is not a problem with the design. No matter how you --

DR. MELLORS: No, but it's a problem with the disease.

DR. HAMMERSTROM: Yes, but you don't introduce that problem by using a mild factorial. It's a problem, no matter what. You may not be able to identify in time to do anything. No matter how you're testing the drugs, the disease is what it is.

DR. MELLORS: Right, right.

DR. HAMMERSTROM: Trial design cannot correct it.

DR. MELLORS: But setting up for adding when you have the possibility of two companies who want to get together or three companies and then randomizing somebody to getting only one of those investigational agents.

DR. HAMMERSTROM: No. The only ones we're considering are -- well, if there is two, you would get one. And if there are three, you would get at least two.

DR. MELLORS: Okay.

DR. HAMMERSTROM: I don't think

practically that the three-way drug is going to come about. I think that, not for statistical but for logistical reasons, is highly unlikely.

DR. MELLORS: Well, it's likely to. And so you're randomizing people to one. It's likely that two will become available more likely than three.

DR. HAMMERSTROM: Right.

DR. MELLORS: And you're randomizing people to one with this, quote, "quick bailout."

DR. HAMMERSTROM: That's better than randomizing to none.

DR. MELLORS: No, it's not, not necessarily.

ACTING CHAIRMAN GULICK: Dr. Jolson?

DR. MELLORS: You basically don't understand the pathogenesis of the disease. You only get one shot with the drug if resistance develops.

DR. JOLSON: Let me make --

ACTING CHAIRMAN GULICK: Dr. Jolson?

DR. JOLSON: -- just one point of clarification that I think needs to be understood that any time we're talking about optimized background therapy for either a factorial or a straightforward design, we are assuming that those patients have access to other expanded access drugs. That's

implicit.

So when we say one investigational drug, that's not quite true because they have the opportunity to enroll in other expanded access programs. I think that's what some of the disagreement was about.

Let's just assume because we've gone on record as saying this that when we talk about optimized background therapy, we are assuming that it's your best combination of drugs with whatever resistance testing is available to help construct that plus whatever expanded access agents are available that are not the subject of the research question in the study.

ACTING CHAIRMAN GULICK: Dr. DeMasi, waiting patiently.

DR. DeMASI: I'll just make a point about the role of factorial deigns in potential drug development and, again, distinguishing between a registrational trial and a strategy or three before even Phase II study in which you had a factorial but you were looking at the additive contributions of activities of regimens early in the treatment period, say one to two weeks.

The second point is that in terms of a

modified two-by-two factorial, if that was the case where you had AB and AB in the presence, one of the assumptions of the factorial designs is assumption of no treatment interaction.

So positive or negative interactions may complicate the interpretation of the main effects of drugs A and B. If this is a pivotal study, how would that be viewed in terms of the individual drugs?

DR. HAMMERSTROM: Well, most likely the interaction will be positive. You get more from A plus B than the sum of what you get from A and B alone, in which case there is no problem at all as long as A plus B beats either A -- if it beats A, then B is contributing something. If it beats B, then A is contributing something. That is all you need for registration.

ACTING CHAIRMAN GULICK: Mr. Hogan?

MR. HOGAN: I'll try to keep this very brief. I'm going to throw in a minority viewpoint. I realize this is very controversial. We all know that for most of the toxicities, your risk of a toxicity goes up as you progress in the disease.

Even in this era of sort of the resurgence of OIs, my physician is telling me he is still treating five toxicities for every OI. Keith Henry

went on record as saying he is doing 20 hospitalizations for toxicities for every hospitalization for HIV-related condition.

So, to my mind, I think closing the door on that no-drug factor or that one-drug factor may be precipitous. I think that there may be some situations where we may examine whether actually taking drug is harming people. I think that is an important thing.

I am not speaking for the Coalition for Salvage Therapy. This is not their perspective. But I think it is important to actually look at what the minimum amount of drug it takes is, as opposed to the maximum amount of drug that can be tolerated.

ACTING CHAIRMAN GULICK: Dr. Schapiro and then Dr. Pettinelli.

DR. SCHAPIRO: I do think we have to make a little bit of a reality check here. Mike, of the 70 patients who died, how many of those did not have optimized therapy?

DR. SAAG: At the time they died?

DR. SCHAPIRO: Yes.

DR. SAAG: Over half. I mean, actually probably 80 percent.

DR. SCHAPIRO: Were not optimized?

DR. SAAG: Yes. I mean, in other words, those were people who have been through everything. It depends what you mean by optimize. They certainly are not below the level of detection. There were none of them. Well, I take that back. There were some who died of toxicities. So they were below.

DR. SCHAPIRO: In these study designs, how would you have optimized? You know, we're optimizing, then giving all of these things. We're fooling ourselves. You were doing, I would assume, as best you could and they were still dying.

I think most of us -- and I think we are going to see more and more of it over the next year or two -- are optimizing therapy. And, despite the fact that we're optimizing therapy, --

DR. SAAG: Oh, yes. And they don't respond.

DR. SCHAPIRO: -- resistance assays don't help us if in options.

DR. SAAG: Right.

DR. SCHAPIRO: So these patients I think probably in Steve's clinic, in my clinic, I try to optimize them. I can't because they are optimized and they still are in bad shape.

DR. SAAG: In which case in those

situations, mono therapy may be an option, even though pathogenically it's not what you would want.

DR. SCHAPIRO: So I think we have to step one back. You know, I also have designs on my slide to say: We'll optimize and so on. But in real life, when we try to take it, maybe that's what Steve is saying is not going to happen because that's not what's happening.

The patients are optimized. We do use, many of us, resistance testing. And many may use it in the future. We're doing all of the other techniques we can, and they're still dying. So these designs look good. But basically for these heavily pretreated patients, they are optimized. That's not the issue.

The other issue is we may not have together three drugs. And we can't probably wait six months to get three drugs together. So if we want to get really real about it: one, the patients are optimized and, two, we don't have two or three agents to combine. I think that we should take into account.

I think to get back to Dr. Jolson's question, what do we want to look at for efficacy in these patients, I don't think we will be able to look at it well in these patients. I don't think you will

be able to get an answer in the heavily pretreated patient, which basically are the patients who we're most concerned about I think that Mr. Hogan also mentioned. You cannot do good studies.

Now, I think what characterized those patients most -- and many things characterize them -- is the fact they have resistance. I think the one barrier that usually precludes our best management is the resistance. Adherence and toxicity are important, but I think if I could change one thing in a patient, I would give them a wild-type virus again.

I think we may need in some cases in those patients to use the resistance as a surrogate. So we will not be able to say, "Does this drug work well in heavily pretreated patients?" because we can't do good studies. You know, there's nothing to optimize and no three drugs to debate because they got them already.

What we will have to do is say in other patients we're maybe one step back or two steps back. Try to characterize how those drugs work with specific resistance patterns.

I would, again, you know, what I always plug, we have to see with which exposures they work. And then we'll be able to say we don't know specifically how this works in those patients, but if

you show me what their resistance profile there is, what fall change there, what mutations they have, from patients who are less experienced, we can tell you that if you give this dose, you will have some response.

And then we'll be able to say, as Mike and Steve -- I mean, you'll probably get half a log. That's good. I think in reality, for those heavily experienced, we may not be able to do better than that.

ACTING CHAIRMAN GULICK: Dr. Pettinelli?

MR. LEVIN: Are we going around or not?

ACTING CHAIRMAN GULICK: Yes. I'm keeping a list, Jules.

MR. LEVIN: We're not going around? We're just going by hands?

ACTING CHAIRMAN GULICK: That's correct.

DR. PETTINELLI: I think, again, the issue is the definition what is the heavily pretreated. For me, when I'm talking about optimized therapy, at least the patients should have access to two drugs for which the patient has sensitivity.

They could be new drugs. They could be old drugs. It also depends again on what is the viral load of the patient. A patient with 30,000 copies of

virus must feel a very good response from their therapy.

So, really, I think there is the possibility to study the patient. We need to define what is the population. We might need to use probably the modified factorial design because, really, I'm not sure that all the time A plus B is better than A or B. That's a big issue for us. Combinations do not always depend.

Now, again, there may be overlapping toxicity. And there may be issues there.

ACTING CHAIRMAN GULICK: Dr. Mathews?

DR. MATHEWS: You know, there was a time in the development of HIV therapeutics where there was considerable reluctance for sponsors to study very late-stage patients.

And I remember some presentations at this Committee showing that you could actually measure clinical endpoints in people with less than 50 CD4 cells and show that a drug worked.

We're beyond that by several years now, but in a sense, when you're faced with a patient who is resistant to everything on the panel and has a very low CD4 count, it's a high-risk situation, not only for the patients, who might be considering entering a

trial, but I would think for a sponsor.

We have seen some examples where drugs which were not home run drugs that had moderate or modest activity could be severely compromised in their development programs by their performance and some pivotal trials of the nature of which the previous discussion has been focused on.

I don't for one think that patients should be trapped into enrolling in clinical trials simply to get access to drugs. And I think if we're realistic about it, both to meet the needs of industry as well as patients and their doctors, we would focus more of our efforts in the treatment-experienced populations, not to the people who have bars across the page on the resistance profiles for enrolling in salvage trials.

But I think people more along the line close to the definition that the agency put up who have some resistance have failed some regimens, perhaps some in all classes, but not completely exhausted all therapeutic options.

I think those patients should be immediately offered access through expanded access programs so that toxicity data can be collected and that the salvage trials should be focused on people where a measurable effect can be easily seen.

ACTING CHAIRMAN GULICK: Dr. Saag and then Mr. Levin.

DR. SAAG: I wanted to clarify a comment I made. What I'm saying, you evaluate for safety and activity. There is a tension between how long do you follow up before you let the drug be approved versus how long do you follow up afterwards. It's the point Carlton made about holding people's feet to the fire for long-term follow-up.

So what I'm referring to is short-term safety. Lynda, I'm not talking about cardiovascular things or lipids necessarily because they may take longer to develop.

The point is that you have to decide if the drug is active and it's relatively safe, then you get it out. But then there is an obligation to follow it up.

The problem in my mind in the follow-up -- and I realize I'm a little bit off topic, but I'll be brief. The problem with the follow-up is that in my opinion Phase IV studies in HIV are dead.

You can't do them because by intent to treat, by the heterogeneity, you can't follow from that original new regimen that might last three months. How do you follow out for two years?

What you need is cohorts. You need to follow cohorts carefully, accurately. In my opinion, that's where money ought to be spent,min capturing real world data on experience and exposure to multiple agents followed over years, hopefully decades. And then we can have some way of doing that.

So I think that is where industry ought to work together to establish mechanisms to follow these patients in that way. That's a whole separate topic, but it is germane because I think we do want the drugs approved quickly and get into expanded access quickly once their profile is determined, as least in the short term, that it's not doing harm and that there is some benefit.

ACTING CHAIRMAN GULICK: Mr. Levin?

MR. LEVIN: To be honest with you, I'm not sure what we're doing here today and, really, the productivity of this discussion. I agree. When we're talking about deep salvage here, people who have very little, if any, options left, I agree. I agree with Mike and with Steve and particularly -- is it Dr. Mathews? -- in his last comment. We're talking about, really, access to new therapies, no matter how you get it.

The only reason to do a study for a deep

salvage patient to go into a study is to get access. If we could get it through expanded access, well, that would be fine, but that's not happening.

Now, having said that, I also feel it's extremely important to try and capture toxicities and side effects. So I want to try and make a few comments here.

I think that what we need to do is to try and get -- the problem is here that you don't have A, B, and C, as already said by several doctors here. You don't have A, B, and C available. There is no A, B, and C.

Next year there will be hopefully DAPD. Right now we're talking about T-20. There's no A, B, and C at the same time. That's already been repeated by several people. I said that an hour ago.

There is no A, B, and C to even do the factorial design. There are no three new drugs available right now. Tipranovir is not available. DAPD is not available right now. We're talking about next year maybe.

DR. MURRAY: It could be. We're trying to get collaboration together. We're trying to bring forward drugs together. I would hate this meeting to end with sort of the companies getting off the hook of

working together with drugs that are not available yet on expanded access.

There are lots of drugs in Phase II development. There are more than three drugs. Right now we don't have any expanded access. So I think if you have a lot of drugs in expanded access, a design like Dr. Mellors', maybe it would be preferable. But when you don't have expanded access and you want to bring Phase II-ish drugs out so that they can be studied together, I would think that there would be some benefit to a modified factorial design.

And companies would each benefit because they would potentially get to use that data to support registration. If they just have to give a drug to be a co-drug with another sponsor who is investigating their drug, I mean, what is their incentive?

What we're trying to do here is given incentive to get drugs out together in combinations in which they might not be used until expanded access. I think we're trying to do that sooner and we're trying to provide them incentive to do that.

I hope that we don't go away from the table today with pharmaceutical sponsors not hearing that. Is that what you want or not?

MR. LEVIN: Let me just finish. I agree

completely in a deep salvage situation. Let me try to answer the question a little bit that is being posed by the FDA. I want activity identified.

And then I agree with Dr. Mellors. I am a person with HIV for 18 years. I'm in the community. And my community perspective is that I don't want one new drug.

I understand there are concerns about toxicity and side effects and so forth. We have no perfect answer here, and maybe we need several studies. I don't agree with just adding on one new drug, and I'm not so sure.

So I think that for a deep salvage situation, we probably need two or three drugs. And what is available ought to be used by that person once we clearly identify activity, which is important to me.

ACTING CHAIRMAN GULICK: Dr. Jolson and then Dr. Pomerantz.

DR. JOLSON: I just want to follow up on a comment from Dr. Mathews and also Dr. Schapiro. It was never our intent in this meeting -- and, in fact, if you notice, we don't use the word "salvage" therapy. We're really focusing on drug development for treatment-experienced patients.

I just want to make certain that our entire focus today isn't on what has been referred "deep salvage," even though there is no question that those are patients in desperate need, because recall now that we have drug labels.

We have 15 approved antiretrovirals. And the kind of data that's in the labels is in treatment-naive patients or nucleoside-experienced or first PI failure. We don't even have the data that would fit the definition of what we're talking about.

So, even though it is not going to meet the needs of everybody, it would still be an improvement over currently available information to have data on the patient populations that would fall within our definition.

We really need help to do that because they aren't patients who maybe have exhausted every single option. They have exhausted, though, many options. And it's not clear because of the imperfections of resistance testing, particularly for PIs, you know, what are going to be viable drugs.

So I know everyone has focused on the worst case scenario because it is a desperate need, but we would be happy to see drug development as the next step to just include patients who have three-drug

prior experience.

ACTING CHAIRMAN GULICK: Dr. Pomerantz?

DR. POMERANTZ: Yes. Thanks. I was actually talking to Dr. Stanley. I thought I would say it into the microphone.

I saw a couple of hours ago this discussion start digressing into two groups that Mike and Dr. Mellors tried to pull back. And it came back again with Dr. Mathews now. People have been discussing at cross purposes there is clearly the group that the FDA had started our discussion with, which are those patients that have gotten two failures of HAART regimen and have seen all three classes of drugs.

Then there are the ones that are non-quantitatively described as either deep salvage or someone who has an Andromeda strain bug with diverse mutations that nullifies virtually everything that is available. Those are different.

I think that was the problem this morning. And I agree there was a problem. This is a very difficult discussion. It is also a terrible part of the literature to read. It is scientifically dirty because it is so complex. And we're just beginning to tease that out.

I think it is very important that as people discuss how they want to design trials, they discuss whether it is the first group that the FDA started with or the last group that we digress to at times.

Those patients usually get what I call the end group that have nothing available to them, have any profoundly low CD4 count, and have a pretty high, whatever you want to define that, RNA load. They get a "Throw the kitchen sink at them" philosophy.

And that is no one is going to enroll those patients in the real world for a study if they think they have the advent of a horrible opportunistic infection or death within a certain period of time.

I think you have to decide how you want to treat the first group, which are those that are more amenable to study design. I like to see John shaking his head because the other group is going to be very difficult to study and will be studied later down the line when you know more about the toxicities if they're studied at all.

Now, the other point I wanted to make is why I think this is an interesting, yet scientifically dirty subject. And that is some of the stuff that Dr. Deeks has taught us has been really profoundly

interesting. And that is the patients in this group that have failed a couple of times that then get a half a log effect on viral RNA but do well or the discordance that you see at times, even long-term, between CD4 and RNA levels.

I think about this like the Committee might have thought about resistance testing five or six years ago. Now we're dealing with possible different viral quasi-species, different strains.

No one has mentioned the bugaboo term of "fitness," but that has started to be developed as an indication of why certain of these people may do better than others at the same viral load.

Dr. Mellors does some of this work. Dr. Dequilla has had a nice study. And fitness is not just replication, but it should better be defined as virulence.

So I think that what you should try to dissect out of these studies is those that you can really study. Right now I think it is where the FDA put those terms at the beginning, which is going to be hard enough. At the same time, try to dissect out the scientific meaning for the dirtiness of the findings in this complex group.

ACTING CHAIRMAN GULICK: I'm going to

take two more comments: Ms. Delph and then Dr. Mellors.

DR. DELPH: Thanks. I won't reiterate Dr. Pomerantz's point, which was going to be my first, that drug companies are not going to enroll patients who have no options left. It doesn't make sense, and they just won't do it. It is not going to be to their benefit.

My other point is that while I think it will be difficult to get companies to work together, I think we are here to discuss scientific issues and scientific validity. I think we are here to give the FDA advice on how to proceed, our best scientific advice, and to ask the FDA to take that scientific advice and try and get the companies to follow that scientific advice in their registrational studies and not simply to start off by saying, "Oh, well. The companies won't get together. They won't do it. So let's throw factorial designs out the window."

From what I have heard, factorial designs seem to be one of the better scientific options in my opinion, probably the best that I have heard, the modified factorial.

I think we would be failing in our duty if we simply threw it out the window, as scientifically

sound as it is, because we don't think we can get the companies to work together.

ACTING CHAIRMAN GULICK: Dr. Mellors?

DR. MELLORS: In an attempt to -- I mean, it's good to break apart and have differences of an opinion. In an attempt to form a better union between this side of the table and that, let me say that the factorial design -- Roger said this nicely. My comments about the factorial design were directed towards patients who have a limited life span and desperately need more than one investigational agent. Okay?

I don't want to see the agency say, "Well, you have to do factorial designs in this population." In the less advanced, less desperate population, the factorial design does provide some efficiencies, particularly the modified factorial design.

And I would just like to throw it back at the agency. Are you totally comfortable with a modified design that excludes the, quote, "double" placebo arm or control arm that you can tease out the individual toxicity of each component in the trial if there is an interaction and the gating interaction potentially between toxicities in the A plus B cell?

DR. MURRAY: It's no different from

looking at something that might include low dose or ritonavir. Who knows what that is going to do to the PK and the toxicity or any other drug, for that matter, a delavirdine or efavirenz, which might, you know, induce?

The problem is not unique to factorial design. It's a problem of combination studies. There is a risk of not being able to tease out. There is a risk of any study failing. But I don't think it is more in the factorial than in any other combination study.

DR. HAMMERSTROM: All of the designs we've been doing since the first two or three drugs came on have always been new drug A plus X where X is a collection of drugs that have already been approved versus X alone or versus X plus Y, where Y is a known active agent, whether you're doing superiority or equivalence.

So it has been a long, long time since we have ever had an ability to look at only what new drug A does in the absence of anything else. There is always something.

Everybody for the last four or five years, all the trials, drug A has always been added onto other drugs, most of which are known to have

toxicities and have contributions. And, in fact, the inference we're making is that, let's say, if you add nelfinavir to 3TC plus AZT and you get a benefit relative to what AZT and 3TC alone would give you, then when you add nelfinavir to other combinations that may not include either AZT or 3TC, we expect you will probably get a benefit. But that inference is not based on observational data.

Certainly the FDA does not require the study of every conceivable one of the -- there is now 2^{15} power with 15 agents -- actually more of that because the number of different two, three, four-drug combinations you can make now with approved agents is somewhere like a million. So we don't study all of them.

DR. JOLSON: Just as a final point, it would be rare for us to look at a study in isolation. We're going to look at it kind of in the collective database.

For many drugs, there may be other study designs that would be more straightforward that could provide additional safety data. This would just be one more piece.

ACTING CHAIRMAN GULICK: Let me try to summarize the discussion briefly. There was a

consensus around the table that treatment options in this particular patient population are very much needed.

We recognize that this is a heterogeneous population. It is an advanced population in some cases, quite challenging, critically ill, and in some cases with a high risk of mortality and few options for treatment.

Several people noted that there are subsets of patients within this patient population ranging from people who do have options to those who have no options at all. It is worth pointing out that often the group with no options is the one that needs the options the most.

As an objective for our studies, we want to identify drugs or strategies which result in virologic and immunologic improvements, but our ultimate goal is really to improve clinical endpoints; that is, survival and health. Another objective is maximal access to agents which could have these positive effects on virologic, immunologic, and clinical endpoints.

Testing in this population is challenging. And there is a basic conflict which I think came out in the discussion between trying to show the

individual drugs' efficacy and safety versus coming up with a strategy which will actually have benefits in this challenging patient population.

I think we agreed around the table that you need to start by optimizing the background antiretrovirals as much as that is possible using resistance testing and allowing access to all available agents, both approved and expanded.

There was a feeling that it may be reasonable to tolerate a higher incidence of toxicities in this patient population. And it was pointed out more than once that weighting for new drugs may not be an option for some members of this population.

In terms of a conventional registrational, people agreed that we still wanted to see antiviral efficacy. Some suggested as short as 10 to 14 days with a drug would be sufficient as mono therapy to try to decrease the emergence of resistance.

Safety. People felt that longer data was needed, 24 weeks being standard or even more. Along with registrational development, people felt a comprehensive approach was appropriate, that some of the supportive data that we would like to see is increasing doses in this patient population, a frank

dose-responses curve using PK enhancements to try to overcome resistance, defining drug-drug interactions earlier in drug development, particularly with these patients who are on multiple other agents, and assessing viral fitness in this particular patient population.

Some of the novel designs that we talked about today: single arm, with or without historical controls; an early versus delayed introduction of a new agent; using a crossover design with the same early versus delayed; differential randomization, either two to one or three to one, among certain arms.

An early switch if the drug is shown to be ineffective was another strategy mentioned. We spent a lot of time talking about factorial and modified factorial designs. I won't reiterate the points made there. And, finally, long-term cohort studies in this patient population were all mentioned.

Finally, I think there was a consensus around the table that we would like to see some pressure put upon the pharmaceutical companies to work together, particularly in this patient population, that the number of drugs available at any one time may be limiting, although, as was pointed out, there are many in Phase II of development; and, finally, that

expanded access may be the only hope for many of these patients and that we should encourage earlier development of these programs.

With that, I would like to have us break for lunch. It is 25 of 1:00. We will reconvene at 1:30.

(Whereupon, a luncheon recess was taken at 12:36 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:35 p.m.)

ACTING CHAIRMAN GULICK: We'll get started again. Welcome back from lunch. We would like to start the afternoon session. Dr. Jolson would like to make a couple of clarifying remarks based on the discussion this morning.

DR. JOLSON: The discussion this morning was fascinating. It's probably worth mentioning that you all are here at a two-day meeting. We realize that there is a lot of material to cover. We would have even had this as a two-day meeting except for the fact that there was an NDA that needed to be discussed yesterday. We thought that three days would be kind of dicey at the beginning of January. So it doesn't surprise me that it really took several hours to work through and highlight some of these dilemmas.

I just want to, though, just reorient us because I think we have identified both population differences and differences in clinical needs for different populations and again ask you as you think through the next series of questions to perhaps broaden your discussion to include patients who are treatment-experienced but who aren't necessarily the very illest patients and because we believe that

current drug labels and future drug labels would be greatly improved by inclusion of those clinical trials. We think that those trials are more likely to be done, particularly for registrational purposes.

And while we totally acknowledge the need for treatment options for the illest patients, we also agree with some of the comments earlier this morning that it would be extraordinarily difficult to do comparative trials.

So that isn't necessarily where we as folks who advise on drug development are necessarily putting all of our attention. There is plenty of room for improvement in current drug labels. And we ask you all for your thoughts on clinical trials that would provide that sort of information.

ACTING CHAIRMAN GULICK: Thank you.

OPEN PUBLIC HEARING

ACTING CHAIRMAN GULICK: We're now going to enter the open public hearing portion of the meeting. We're going to take the listed speakers somewhat out of order. The first speaker will be Emmanuel Trenado, who is a member of the Coalition of AIDS Organizations in France. I just spoke to him. So I know he is here. Oh, there he is.

MR. TRENADO: Good afternoon to all of

you. I am here only to commend the EMEA proposal on the new points to consider to register new drugs for patients who fail all existing regimens.

So I only have four slides, and I'm going to be very short and will leave it to Daniel Vittecoq, who is a member of the EMEA, to present you the points to consider.

The background in Europe is a bit different than what you have been experiencing here in the U.S. In Europe, expanded access programs because we are so many different countries are run very differently from one country to the other.

For example, a drug such as Ziogen took a year and a half. It had a year and a half delay compared to access in the U.S. for countries such as Italy. France was faster, but some of the European countries, it takes longer to open up those expanded access programs. And there is this particular situation.

We all share this common dramatic situation where we are in great need to have access to new drugs. And this is particularly the case in Europe.

The new points, the AIDS community in France and in Europe have taken on both the new points

to consider as a way to accelerate access to new drugs in the whole of Europe.

Next slide. So we have commented on the proposals. And we made a few remarks. We have a proposal to make to the EMEA. The first remark concerns the mono therapy phase trials.

You will see in the details what the EMEA is proposing, that the community feels that the mono therapy trial should be differentiated according to the drug that is being investigated. And it should be as short as possible.

Then you will see that the EMEA has come up with the idea of selecting refractory and non-refractory patients who are in need of salvage therapy. And they feel that registration trials should only be run in patients who have treatment options. So they are called the non-refractory patient. And we agreed to that proposal. We have seen it this morning. We think it is very difficult to run ethic trials in patients who are in deep salvage situations.

Next slide, please. So the proposition we would like to make to the EMEA is that while the industry might be selecting the patients to enter those Phase III trials, it's like on the resistance

testing to do so. And they are separate, the patients in two groups: the refractory and the non-refractory patients.

We feel that the patient who will be labeled "refractory" should have access if they want to to the drug that is being investigated outside of the clinical trial in an expanded access program.

And we feel that this should be made compulsory to the industry, and it should be inserted in the registration package, that the drug should be made available in refractory patients who have tried to enter the Phase III trials. And they couldn't get around saying, "There's no drug. We could not open up this expanded access," et cetera. So this is a proposal, the main proposal the community is making to the EMEA.

The last point is on pharmacovigilance. We know that in some European countries, pharmacovigilance is not running very well. And we feel like that it should be an occasion to really rectify and to set up a European plan to improve pharmacovigilance in Europe.

Thank you very much.

ACTING CHAIRMAN GULICK: Thank you.

Our second speaker is Dr. Otto Ah Ching

from Oxo Chemie. He will be using a remote mike.

DR. CHING: I would like to thank the Committee for the opportunity to be able to speak with you. I don't have slides today. Basically I would like to address some questions.

Oxo Chemie now is engaged in a Phase III trial currently with our IND and with the FDA currently. I have three specific questions I would like to address to the Committee if possible, one being historical data with HAART as standard of care has shown that CD4 and viral loads in these populations with AIDS demonstrates some significance with little sustained changes. Should the Committee consider a more prognostic measure or marker? Heaven knows we don't need another surrogate marker. But would they be open to considering CD38 as a possible prognostic marker in salvage therapy?

The second question is immune-based therapy. In salvage therapy, what standards will determine efficacy and safety if these therapies are not antivirals? Should we then look to more of the clinical benefit and clinical endpoints weighing heavily more on the clinical benefit for these patients, rather than surrogate markers or lab surrogate markers?

And the last question is: In salvage therapy, should these studies be open label and comparative with historical data as standard of care measuring induction period to onset of primary SAE or AIDS-defining event and resolution?

I think these are just basically three questions that we as a company wanted to present to the Committee and get some feedback on. And that's all I have to say.

ACTING CHAIRMAN GULICK: Thanks very much. I hope to address some of your questions in the discussion period later this afternoon.

The third speaker is Mr. Michael Marco from the Treatment Action Group.

MR. MARCO: Good afternoon. I am Michael Marco from the Treatment Action Group.

This morning I heard a rumor that Dr. Jolson was going to be leaving the agency. I wanted to let Dr. Jolson know that TAG has a job opening and that you can see me after the meeting for an application.

(Laughter.)

MR. MARCO: We do like your work. And TAG thanks you and your division for putting together this meeting. The last time I was here and talking to this

Committee was at the adefovir hearing. That was a sad day. As we know, it was the first time that the agency did not approve an HIV drug.

Today is a much better today. It's a brighter day because now we will be looking at trial designs and hopefully agree on some trial designs where we can help salvage patients, the ones who most need it.

Today is also a day where industry can stop saying that the FDA does not give them a clear message. Time and time again they tell the community "We don't know what the FDA wants. We get mixed messages." Hopefully they will hear loud and clear and through more discussion, things in writing that the agency puts out, they will know what to do for trial designs.

Most of you have the position paper that TAG wrote. At least I know the Committee does. Some of you in the audience do. I have a few extra.

The position paper will be available on the TAG Web site. It will be available on Monday. And the Web site address is basically www.treatmentactiongroup.org. It's all one word, treatmentactiongroup.org.

I won't go through the position paper.

It's four pages. You can all read it. It's very clear. I will tell you that we come away with supporting the modified factorial design. We do believe that it is an excellent design. I think we will hear a little bit from Dr. DeGruttola, who will explain why it can be so beneficial in this patient population.

Today we heard that there are not that many drugs or really no drugs or only one drug and so how could we do modified factorial design. Well, I know of at least four drugs that are around Phase III right now. We're in Phase III. We have the three T-drugs, and we have the BMS protease inhibitor.

These companies are rapidly developing HIV drugs. That's why they need to be getting together now or even before they go into Phase III so that we can get them together to agree on a modified factorial design.

And the FDA will need to give clear incentives. The FDA will need to help them out and also probably be somewhat gentler in the labeling because we won't be able to tease out all of the various toxicities.

In the modified factorial design, it is important to note that a lot of patients won't be able

to go in the study and a lot of patients won't be able to go into any of the studies that the FDA presented earlier. Many of these patients, especially the ones that Dr. Deeks talked about, only have ten CD4 cells. They cannot put together an optimal background regimen.

Many of the studies now that use the term "optimal background regimen" say you need to be susceptible to at least two drugs. For these patients, we need to make sure that they are the ones that first get the drugs that are out on expanded access. And industry needs to be a little more proactive and work more with the community in getting drugs on expanded access earlier, not a month or two months before the drug is approved.

As far as efficacy is concerned, we do believe that for a drug that shows great activity, shows great promise, possibly a home run, if there is such a thing, that 16 weeks might actually be enough for efficacy compared to the 24 weeks that we use now for accelerated approval.

We would say that for safety, we definitely want at least 24 weeks of safety for accelerated approval. And we still want the 48 weeks for full approval.

Lastly, we do need to make sure that, especially for the modified factorial design, PK studies are done. And they need to be done ahead of time with a decent amount of patients. We don't want the debacle that we had with ACTG 359.

I appreciate you having me speak. And, again, I thank the agency. And I hope that the afternoon is just as contentious as the morning was.

ACTING CHAIRMAN GULICK: And I think you can count on that. Thank you, Mr. Marco.

The last two speakers will be using slides with their presentations. And that is why we have put them last. Next is Dr. Vittecoq from the EMEA in France.

DR. VITTECOQ: Mr. President of the Advisory Committee, members, Mrs. Jolson, and Jeff, thank you very much to provide the opportunity to the EMEA in Europe to give you the guidelines which have been adopted or will be adopted in the next month by Europe.

Maybe just before starting, for the CPMP members, you have to know that the research for such drugs, which is very important from a public concern in Europe, is not a national procedure nowadays. It is in Europe. This is orchestrated by the European

drug agency and a special committee, which is a CPMP.

So there was a debate at the CPMP last year about the evolution of the AIDS epidemic. And it was concluded that, despite substantial improvement, there was still an increase in the number of patients who failed the treatment. And this was where the public was concerned.

As it was told previously by Emmanuel Trenado and as a problem in Europe is the availability in the early access to drugs in different countries. France has quite a performance at this time, which is a temporary authorization of use of drugs. And most countries do not have any access to drugs. So this is an eventuality which is politically not acceptable.

Another point which was a matter of debate to the CPMP is the length of the trials. In 48 weeks, approval for promising new drugs is not ethically acceptable for patients who are failing.

The last conclusion was that companies are not very inclined to implement clinical trials in advanced patients for various reasons. It's more difficult to reach endpoints. And, secondly, the tolerance of the drugs is not very good in these populations.

So the CPMP asked the French Agency for

the Safety of Health Products to address a proposal which has been a matter of discretion six months ago. And the final paper will be accepted in the next month.

Next. So a few considerations before we improve in the evaluation of treatment because we have given a particular place to very different parameters. And this is a reality that cannot change.

Antiretroviral drugs are not similar to antiviral drugs. Antiviral drugs are not even comparable to all other anti-infective agents, even tuberculous meningitis. New figures of the development of antiviral agents seems to be more closely similar to antineoplastic agents.

In our way of thinking, a patient in failure is like a patient with fatal status. And adding concern, we have to promote the development to reach limited indications in patients with fatal status. And then indications may become broader later on with the case.

The situation of the epidemic in Europe is very different nowadays. This is a perfect relief sentence, but AIDS belongs to the past. That's not where we come as physicians. I know AIDS is 20 years. So some patients are still dying, but the number of

patients and the way to die in AIDS is clearly different.

And I should say as the guy from the CPCRA this morning, I do suggest that we change the term of "salvage therapy," which is not appropriate.

Salvage therapy in AIDS is not a new faction. Salvage therapy started as soon as it was registered, delavirdine, which was 15 years ago. And as soon as patients have failed delavirdine, didanozine was the first salvage therapy. And as soon as patients had received didanozine, optimal modification had been performed.

So, really, the situation now is at treated patients, which can be defined as good responders and poor responders. We have to focus our attention on patients who are poor virological responders.

I do believe in the next future, that we will have to take into account another picture, which is immunological response. Some patients with a good virological response are poor immunological responders, and some are not.

The aim of the proposal is to improve the quality of the registration package, which is not always performance. And the second point is that we

have to anticipate the way the drug will be used. It is not acceptable nowadays to have a drug like saquinavir, which has been used as a mono therapy of protease inhibitors, as it has never been used without ritonavir. And I should nearly the same with amprenavir.

Next. So, to improve the way to treat the patients in these kinds of failures, we have to start I think from the drug. We have a new drug. An applicant is asking the questions, "What can I do if these aren't antiretrovirals?"

We have to insert the main question, which is: Is it a major interest in terms of resistance profile or pharmacokinetic parameters, which is in the Phase I and II trials?

You have two answers, "Yes" or "No." If the answer is no, there is no modification of the guidelines, which are quite performance. And that would suggest maybe to enhance the length of evaluations. Forty-eight weeks maybe is not enough. And maybe in the next future, we have to enhance the follow-up of the patients up to 96 weeks due to a better package for safety.

If the answer is yes, we have to speed up marketing authorizations in antiretroviral-experienced

patient populations. New registrational clinical design, such as identification substitutions, and the time of assessments from our point of view -- I would speak about it -- is less than four weeks. And durability is 12 to 16 weeks.

Next. Major interest regarding resistance profiles nor of few cross-resistance with other drugs in the same family and the unique resistance profile, of course, due to new mechanisms of action is quite easy to understand.

What is important from our point of view is the necessity to test the virological activity on a sufficient number of strains coming from pretreated patients, which is very important and very commonly not enough in the package at time of registrations.

Next. Major interest we're getting from communities when there is no activity since profile. Highly developed plasma and intracellular considerations, of course, may allow to recover in antiviral activity situations. This has been well-demonstrated with ABT 378.

And it's necessary to compare the IC5090 of the antiretroviral to do the other regimens from the same pharmacological class and of the same cell lines, which is not with performing in the package.

Next. Phase II studies. This is very important before you start Phase III studies. I think you have to have an examination of these points. Those examinations have to be well-established in naive patients or even today in uninfected patients and will have to be confirmed in Phase II or III trials through PK monitoring.

It is necessary to study the slope of the decrease of the viral load in relation to the pharmacokinetics. We have learned this with the parameters, of course. Interaction studies, in particular, we found antiviral drugs likely to be combined with the investigational agents.

Next. The choice of the target populations in Phase III trials, clearly we need flexibility. We have to provide guidelines, of course, but we need to be flexible. We have learned that as soon as we have marketed a drug, it will not be used as we had thought it would be used.

So the compromise is to be as much as possible as close to the clinical practice and the necessity to clear assess impact of the new antiretroviral drug. So we have chosen patients having failed at least the first line of a pharmacological class. And these patients have been

treated for a prolonged period with many antiretroviral agents.

Next. We have two possibilities. In early virological failures, we have detectable to moderately increased viral load, less than four logs, or non-responders, which means viral load higher than four logs.

Genotyping and phenotyping would be performed at this line. You have got to perform the loss of ability, of course, for the seven that exist and for the treatment with the other investigational drugs.

Next. The other target populations, which is the refractory to all the available therapy, which is, as we have told you, deep salvage, I think this is the sam thing. We know it is very difficult to perform studies in this population. So clearly efficacy is probably enough.

It is difficult to assess the efficacy magnitude of anyone in these populations. It is difficult for companies to perform studies in these populations with an urgent need of care. In these populations, clearly it is much more important for the safety than for the efficacy of the drug.

Next. The methodology of the Phase III

trial is that of superiority, not in equivalence, a superiority. Design is clear, closer to the current strategy in clinical practice for all treatment-experienced patients. There are two strategy substitutions or intensification trials.

Next. Inclusion criteria: patients treated with stable combinations for a significant period of time. First, we do believe that it is necessary to have a comprehensive failure which is less than four weeks or even less than two weeks but with agents which are likely antiretroviral agents, nucleoside, non-nucleoside parameters.

Of course, we need to have NSL before four weeks. With other drugs, such as different immunovirological agents, maybe longer time can be taken into account.

For the antiretrovirals that we know, if you have no response at four weeks, the drug is not active. So we can perform studies in addition of substitution of the investigational agents to the baseline regimen of authorizations.

And there is an optimization phase which can require 12 or 16 weeks, addition of the other agents in both groups based on registration test and strategic possibilities. Our strategy is to optimize

at baseline.

Next. Shortening the time of assessment allows to speed up marketing authorizations to avoid emergence of resistance in patients enrolled in clinical trials.

It is possible to assess efficacy in less than four weeks, like previously. And that is the same availability of the virological impact and safety profiles required at around 16 weeks.

Next. The endpoints, of course, it's the impact on the viral load, comprehensive percentage of patients that should be presenting at viral load, all demonstrations of an increased viral load between 0.5 or one log between two groups.

Some other endpoints include: the maintenance of control of viral load; of course, the assessment of safety profile; the treatment as to be evaluated regarding the baseline viral load, of course; predictive value of genotypic and phenotypic resistance would be taken into account; and correlation between pharmacokinetic parameters and virologic agents has to be analyzed.

Next. Some points are very important if we speed up the procedure, of course, and if we limit the duration of authorizations. It is not acceptable.

This is very important for the applicants, all of you in this room.

Dropout rate should be very limited. In particular, a short time is not acceptable at this time. We have so many patients. We have lots of follow-up in clinical trials. So dropout rate has to be very, very limited. And explain, please.

Sensitivity analysis should be performed with facing data, of course. A PK/PD correlation should be performed to better understand the failure to treatment.

Next. About the combination of the investigational agents to other drugs, which is not currently reduced, of course, which is the expanded access drugs, it is not credited. It is currently performed on a baseline.

Some drugs are used on a compassionate basis, but you have to ensure from a methodological point of view, of course, that there is no added toxicity, that the integrity of the partner has to be clear, the drug interaction has to be known. No integrity, there is none to occur, of course. The partner has to be well-balanced in both arms. And, finally, we suggest strongly a stratification.

Next. In conclusion, a new approach in

the evaluation of anti-HIV drugs are allowed to increase the number of available drugs in patient populations, of course, to focus the research on antiretroviral-experienced patients.

When drugs will be reduced with limited indication at the beginning, one may assume that the indications will become broader later on, of course. This means close collaborations between companies, research in situations as authorities in patients, of course, implementation of Phase IV trials regimen strategies used, for example, in Phase IV pharmacokinetics monitoring.

And, to close, we have to have close collaborations, which is, of course, very, very important. And, of course, if there are close collaborations between Europe and the States, it is probably better.

Thanks.

ACTING CHAIRMAN GULICK: Thank you, Dr. Vittecoq.

The last person to speak at the open public hearing signed up to speak is Dr. Jim Rooney representing the Intercompany Collaboration, the ICC.

DR. ROONEY: Thank you, Dr. Gulick and Committee.