UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE

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MEETING

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THURSDAY,

JANUARY 11, 2001

The meeting was held at 8:30 a.m. in the Versailles Rooms I, II, and III of the Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, DR. ROY M. GULICK, Acting Chair, presiding.

PRESENT:

ROY M. GULICK, M.D., M.P.H., Acting Chair
COURTNEY V. FLETCHER, Pharm.D.
PRINCY KUMAR, M.D.
WILLIAM CHRISTOPHER MATHEWS, M.D., M.S.P.H.
ROGER J. POMERANTZ, M.D.
SHARILYN K. STANLEY, M.D.
BRIAN WONG, M.D.

TARA P. TURNER, Pharm.D.
Executive Secretary

CONSULTANTS PRESENT (voting):

WILLIAM BLACKWELDER, Ph.D.
MICHAEL SAAG, M.D.

PATIENT REPRESENTATIVES (non-voting):

LYNDA DEE, Patient Representative
YVETTE DELPH, M.D., Patient Representative
RALPH DeMASI, Ph.D., Industry Guest
JULES LEVIN, Patient Representative

GUESTS PRESENT:

COLEEN K. CUNNINGHAM, M.D.
STEVEN DEEKS, M.D.
VICTOR DeGRUTTOLA, Sc.D.
JOSEPH ERON, M.D.
JUDITH FALLOON, M.D.
CARLTON HOGAN
JOHN MELLORS, M.D.
CARLA PETTINELLI, M.D., Ph.D.
JONATHAN M. SCHAPIRO, M.D.
MARTIN T. SCHECHTER, M.D., Ph.D., FRCPC
DOUGLAS WARD, M.D.

FDA REPRESENTATIVES PRESENT:

TOM HAMMERSTROM, Ph.D.
HEIDI JOLSON, M.P.H., M.D.
KATHERINE LAESSIG, M.D.
KIMBERLY STRUBLE, Pharm.D.
JEFFREY MURRAY, M.D., M.P.H.
DIANNE MURPHY, M.D.

PUBLIC PRESENT:

OTTO AH CHING, M.D.
MICHAEL MARCO
JIM ROONEY
EMMANUEL TRENADO
DANIEL VITTECOQ

I-N-D-E-X

I-N-D-E-X (Continued)

P-R-O-C-E-E-D-I-N-G-S

(8:34 a.m.)

CALL TO ORDER/WELCOME

ACTING CHAIRMAN GULICK: Good morning. I'm Trip Gulick from Cornell. I'm the Acting Chair today. I would like to welcome everyone to this meeting of the Antiviral Advisory Committee, where we will be speaking about HIV salvage therapy.

I would like to start with introductions of the Committee members. Please state your name and your affiliation. And I would like to start with Yvette Delph, all the way down in that corner.

INTRODUCTION OF COMMITTEE

DR. DELPH: Good morning. I'm Yvette Delph from Silver Spring, Maryland. And I work with the Treatment Action Group, a community-based activist organization.

MS. DEE: Hi. I'm Lynda Dee, and I'm from AIDS Action Baltimore and the Treatment Action Group.

MR. LEVIN: I'm Jules Levin, the Executive Director of NATAP, the National AIDS Treatment Advisory Project, -- we're based in New York City -- and also a community representative on the CCG and the ACTG.

DR. MELLORS: John Mellors, University of

Pittsburgh.

DR. SCHECHTER: Martin Schechter, Canadian HIV Trials Network, guest speaker today.

DR. DeMASI: Ralph DeMasi, Director of Biometrics at Trimeris.

DR. PETTINELLI: Carla Pettinelli from the Division of AIDS, the National Institutes of Health.

DR. FALLOON: Judy Falloon, Intramural NIAID.

DR. DEEKS: Steven Deeks, San Francisco General Hospital.

DR. WARD: Doug Ward. I'm also a guest speaker in private practice in Washington, D.C.

DR. CUNNINGHAM: Coleen Cunningham, Upstate Medical University in Syracuse and a member of the Pediatric ACTG.

DR. SCHAPIRO: Jonathan Schapiro from Stanford University and Tel Aviv University.

DR. TURNER: Tara Turner, Executive Secretary for the Committee.

DR. MATHEWS: Chris Mathews, UC-San Diego.

DR. FLETCHER: Courtney Fletcher, University of Minnesota.

DR. WONG: Brian Wong, VA Hospital in West Haven and Yale University.

DR. SAAG: Mike Saag, UAB in Birmingham.

DR. STANLEY: Sharilyn Stanley, Texas Department of Health.

DR. POMERANTZ: Roger Pomerantz, Thomas Jefferson University.

DR. KUMAR: Princy Kumar, Georgetown University.

DR. BLACKWELDER: I'm Bill Blackwelder from the Biologics consulting group.

DR. HAMMERSTROM: Tom Hammerstrom, statistician, FDA.

DR. LAESSIG: Katie Laessig, Medical Officer, FDA.

DR. STRUBLE: Kim Struble, FDA.

DR. MURRAY: Jeff Murray, FDA.

DR. JOLSON: Heidi Jolson, Director of the Division of Antiviral Drug Products, FDA.

DR. MURPHY: Dianne Murphy, Office Director, FDA. And I want to comment that yesterday this Committee provided an excellent discussion on trial design for antifungals. I hope we hear the same sort of discussion again today.

ACTING CHAIRMAN GULICK: And I have no doubt about that.

(Laughter.)

ACTING CHAIRMAN GULICK: This is one of the largest committees I think that has been convened. In fact, I can barely see people at the end of the table.

Okay. Tara Turner will now read the conflict of interest statements.

DR. TURNER: Thank you.

CONFLICT OF INTEREST STATEMENT

DR. TURNER: "The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

"Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

"Since the issues to be discussed by the Committee at this meeting will not have a unique impact on any particular firm or product but, rather, may have widespread implications with respect to an

entire class of products, in accordance with 18 U.S.C. 208(b), each participant has been granted a waiver which permits them to participate in today's discussions.

"A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

"With respect to the FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

"Dr. Coleen Cunningham would like to disclose that she served as co-investigator on a Glaxo-Wellcome study in 1999. She also received fees from Boehringer-Ingelheim for a virology consultation and a lecture.

"Mr. Carlton Hogan would like to disclose that he is an unpaid scientific adviser to Glaxo-Wellcome, Boehringer-Ingelheim, Abbott Labs, Trimeris, Gilead Sciences, Agouron, and Roche.

"Mr. Hogan's employer, the University of Minnesota, has a cooperative agreement with the NIH. They are the statistical and data management center for a clinical trials network called the CPCRA. Mr.

Hogan works at the CPCRA, which is housed at the Coordinating Center for Clinical Research at the university. He does not directly handle data or see patients. In addition, one of the study sites is currently receiving Combivir as the study drug in one of their trials. And industry has supplied study drugs in prior trials.

"Dr. John Mellors would like to disclose that he receives consulting fees from the Agouron Pharmaceuticals, Glaxo-Wellcome, Visible Genetics, Abbott Labs, DuPont Merck, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead Sciences, and Merck. He also receives consultant fees with stock options from Virco, Novirio, and Pharmasset.

"Dr. Jonathan Schapiro would like to disclose that he is negotiating a contract with Roche to study Fortovase. He received honoraria from Roche for his past lectures on HIV resistance. He has also served as a scientific adviser to Roche and Agouron.

"Dr. Steven Deeks would like to disclose that he has received contracts and grants from Abbott, Gilead Sciences, and Triangle. He is also a research for ViroLogic and Viable Genetics, and he receives honoraria from Agouron, Glaxo-Wellcome, Hoffman LaRoche, Merck, and Bristol-Myers Squibb.

"Dr. Victor DeGruttola would like to disclose that he owns stock in Pfizer Pharmaceutical. In addition, he has a contract with Visible Genetics for data analysis. Dr. DeGruttola has also received consulting fees from Tibotec, Incorporated.

"Dr. Ralph DeMasi would like to disclose that he owns stock in Trimeris.

"Dr. Martin Schechter would like to disclose that he is currently on an arm's-length data safety monitoring board for a trial sponsored by Glaxo-Wellcome.

"Dr. Jules Levin would like to disclose that his organization, the National AIDS Treatment Advocacy Project, receives unrestricted educational grants from all HIV pharmaceutical companies. NATAP also received the Ryan White Treatment Education Grant from HRSA.

"Dr. Joseph Eron would like to disclose that his employer, the University of North Carolina, receives contracts from several major pharmaceutical companies to perform research for which he is listed as principal investigator.

"Dr. Eron also receives consulting fees from Merck, Glaxo-Wellcome, Trimeris, and Triangle. Dr. Eron also receives honoraria from several

pharmaceutical companies involved in development and marketing of antiretrovirals. Additionally, he serves as a scientific adviser to Glaxo-Wellcome, Merck, and Triangle.

"Lastly, Dr. Douglas Ward would like to disclose that he owns stock in Vertex Pharmaceutical. Dr. Ward also serves as a researcher for Glaxo-Wellcome, Bristol-Myers Squibb, Schering Plough, Agouron, Triangle, Merck, DuPont, and Gilead Sciences.

"In addition, he serves as a consultant for Glaxo-Wellcome, DuPont, Abbott, Roche, Agouron, Boehringer-Ingelheim, Vertex, and Bristol-Myers Squibb. Dr. Ward also serves as a speaker for Glaxo-Wellcome, DuPont, Chiron, and Agouron.

"In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement. And their exclusion will be noted for the record.

"With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon."

Thank you.

ACTING CHAIRMAN GULICK: Thanks very much. I would like to turn it over to Dr. Jolson for introduction and opening remarks.

INTRODUCTION/OPENING REMARKS

DR. JOLSON: Good morning. I'm always asked to go first so that I can test out the equipment. So I'm always sort of a guinea pig.

We're really pleased to be able to convene this meeting today. We realize it is long overdue and is probably the most important generally broad scientific meeting that we have convened in recent memory.

In the next couple of minutes, I would like to just sort of state what the issues are that we think there will be general agreement on, talk a little bit about our meeting objectives, define the patient population that we're going to be speaking about today, talk a little bit about historically how we think we've reached this point as an agency and where we think that the field needs to go.

I'll mention what FDA's role and interest and focus is just as a reminder, talk a little bit about how we went about seeking public comment, go over the agenda and acknowledgements for the meeting.

So I tried to list a few issues that I

think most of us will agree upon. And for most of these things, you will hear data later today.

First and foremost, I think we can all agree that the utility of initial regimens, both the first regimen, the second HAART regimen, is time-limited. Our first speaker today, Dr. Ward, will be talking to this point.

Second, I think we understand loud and clear both from the community and as health care providers ourselves that there are insufficient treatment options for heavily treatment-experienced patients.

Thirdly, we are painfully aware that very, very few antiretroviral labels have information on either dosing, safety, or efficacy in treatment-experienced patients. And I'll talk a little bit about why that has come to be in a few moments.

Fourth, I think we can all agree that the development of new agents and their identification as well as subsequent labeling is a major public health priority.

So today's objectives, these are really the broad objectives beyond some of the technical issues that we will be discussing. Fundamentally, we

are interested as an agency in helping to facilitate and promote the development of new therapies for patients who we believe are most in need of treatment options.

Second, we strongly wish to foster collaboration between companies in terms of conducting studies together, jointly developing promising products, and sharing placebos for study designs that would be appropriate.

Third, we're hoping from this large expert Committee that we have assembled today to obtain recommendations that we will incorporate into our either existing or developing guidance documents.

The HIV RNA guidance document is what is currently available on the Web. It has recently been updated, but we would hope to incorporate the advice that we receive today into that general drug development guidance document as well as we would anticipate incorporating this information into our guidance documents that are in development which have to do with resistance testing during HIV drug development and also development of alternative dosing regimens.

We realized as we were planning this meeting that for purposes of discussion, we needed to

put forward a definition of the relevant patient population. because otherwise we appreciated that we would probably spend the better part of the morning trying to decide and come to agreement on a common definition.

There's no question that clinically there are many different ways to define patients who are in need of therapeutic options, but we have put forward purely for purposes of discussion the following definition. And that would be patients who have experienced loss or lack of virologic response to at least two combination HAART regimens and patients who within those regimens have had experience with at least one member of each of the three pharmacologic classes.

Why this definition when so many others could have been chosen? We feel that, as a minimal definition, this would identify patients in whom designing comparative trials has been particularly problematic.

Next slide, please. So how did we reach this point? It's certainly easy to say we reached this point because FDA hasn't done enough. Well, I think that is a little simplistic.

Historically, in fact, we have recommended

that new antiretrovirals be studied in many patient groups and in a very broad population to match the use in actual practice.

We have, additionally, provided for flexibility in what the endpoint is. However, in reality, we are painfully aware that most registrational studies have been conducted in either treatment-naive patients or nucleoside-experienced patients only with very few exceptions.

Why is that when we realize that there are other patients in need of therapy and in need of having data and labeling? One is sort of the practical element that often the treatment standards have evolved since trials, registrational trials, would have been initiated a couple of years ago. That no longer is a good excuse, but that is probably the case for drugs that may have been approved about two years ago.

Second, unfortunately, sometimes the new drug is just not expected to be particularly effective or active in a more experienced population because of cross-resistance.

The third possible reason is really the reason we have convened this Committee, because we will recognize the challenges of trial design and also

data interpretation in a treatment-experienced population.

Next slide. We have thrown out just a few of the challenges that we are aware of from speaking to patient groups and also to industry. Why are these trials so difficult to do? Why do we need a meeting? And why do we need probably the largest advisory committee that we have ever assembled to discuss this issue really speaks to what a challenge these trials are to design and interpret.

One is the heterogeneity of the population. It's certainly easy to put a population definition on a slide, but in reality, as everyone knows, each patient is different and each patient comes with a different history, probably a different resistance profile, and has different treatment needs.

Second, it is difficult enough to put together one regimen that would be acceptable for a given patient, but then to figure out what would be an acceptable comparator for the control group becomes even more problematic.

Third, although traditionally we have hoped to maximally suppress viral replication, that may not be possible with all the therapeutics that are currently in development. So that means we have to

look to alternative either virologic or immunologic or clinical endpoints, but we need to discuss as a group which endpoints are clinically relevant and for any given agent what endpoints are likely to be achievable.

Fourth, we're increasingly aware that additional dose finding is necessary for many products in treatment-experienced populations. I think that we're starting to see more interest amongst industry to do additional dose finding, not just in treatment-naive subjects but also in previously treated patients.

Fifthly, every new drug needs a safety database. Certainly with some of these trial designs, safety assessments will be more complicated because of the additional therapies and lack of clear-cut comparators.

Next slide. Well, where do we need to go? Hopefully we all will agree on this, that we do need new agents that have both acceptable tolerability but also established efficacy. That means you need real data to support their use and what I have in yellow here, the development of novel clinical trial design approaches that we hope to formulate today.

Next slide. So what is our role in all of

this? It has been really interesting as we have had ongoing discussions with community and industry. It has become clear that FDA has a major role to play in bringing forward this issue. And it has been very interesting to see both the community and industry looking to us to kind of lead the way and to put people's minds together to try and deal with some of these problems.

In 1999, we sent a letter to all ID holders, the pharmaceutical sponsors, to articulate that there is absolutely no prohibition against use of more than one investigational agent in either a clinical trial protocol or through expanded access, there had been a common misconception that the law didn't allow that. It is absolutely not true, and we think that this is an important component of most clinical trials in this population.

Additionally, we have increasingly been trying to provide both labeling and other regulatory incentives to promote development. As an example of newer labeling, I would refer you to the newly approved Kaletra label, which certainly has labeling that is somewhat different than has previously appeared with previous drugs when there is data that we think is important for practitioners and patients

to be aware of for use in a more treatment-experienced population.

Other regulatory incentives would be the accelerated approval provisions. Certainly development of drugs for treatment-experienced patients is probably the best use of accelerated approval provisions as well as priority review, meaning a faster time frame for reviewing a new drug application.

I think it was clear in talking to both industry and the community that there was the consensus about a need for an FDA-sponsored working meeting on this topic. After I made this slide, it is not to say that other advisory committees aren't working meetings, that you all don't work at them, but this is one where we are coming to you with very open-ended questions and asking you to do work at the meeting and trying to develop answers.

Just as a reminder, what is FDA's focus? There are many different types of trials. This is always a point of confusion. What does FDA need to put something on the label or make a regulatory decision? Well, usually these are registrational studies, which are also described as the adequate and well-controlled pivotal trials. They are somewhat

different than the equally clinically important strategy studies, which are studies that are more exploratory in nature, which would assess the overall efficacy of a regimen.

The major distinction is that it's the registrational study that would allow us to evaluate the contribution of a given drug. That is the burden that sponsors have in order to put that information in labeling.

But that's not all we're interested in. We're also interested in other trial designs and data collection tools that will provide important prescribing information for labeling. Examples would be dose finding, drug interactions, other special focus questions.

Next slide. In order to plan this meeting, we very broadly solicited public input. And we sent out on October 3rd hundreds and hundreds and hundreds of letters to both industry and to I think several hundred community groups. I want to thank Richard Klein's help with that from the Office of Special Health Issues. We also published a Federal Register notice.

In this letter and letter and official notice, we specifically asked for proposals for trial

design and the role of specific designs, comments on the relevant patient population in need, and baseline stratification characteristics.

We asked for comment on what are appropriate or inappropriate control arms and the result of resistance testing to construct an optimal regimen.

We asked for feedback on appropriate outcome measures, different clinical trial endpoints, as well as any additional comments on special considerations for pediatric populations.

Next slide. And so with that feedback, which you'll be hearing about a lot today, we put together the following agenda. First I would like to thank all of today's speakers, who have come in from, really, around the world to try and hit some of the major high points for consideration before the Committee approaches these very difficult questions.

We'll be starting out this morning with the clinical perspective, kind of setting the stage for what is the clinical reality in the year 2001; then moving on to trial design options for adults, kind of an overview of the trial design science; additional options for consideration for pediatric population; and, importantly, an opportunity to hear

from a patient perspective what are acceptable trial design options.

Following those presentations, our division will present a summary of the many responses that we received from the public as well as our regulatory perspective on some of these options.

Next slide. Of course, plenty of time for discussion. And in the afternoon, we'll start out with an open public hearing. I know that there are several speakers who have signed up and I think will also add significantly to our understanding of the issue.

And then we'll be turning later this afternoon to the issue of endpoints, and we'll be talking about what response rates have previously been in previously conducted trials as well as what some of the important statistical considerations are that have further discussion and questions to the Committee.

Next slide, please. In closing, I really would like to acknowledge the unbelievably valuable input we have gotten from numerous community groups as well as from industry groups that are summarized here.

I read them when they initially came in. And yesterday afternoon, I wanted to refresh my memory. I was just really impressed with the quality

of thought and attention that everyone listed here on this slide brought to this issue and really speaks to the widespread recognition of the importance of today's meeting.

And, lastly, I want to end by acknowledging the folks in our division as well as Richard Klein, who put together this meeting and have really worked very hard, in addition to doing all of their usual work, to bring forward what I think will be a very productive discussion and informative for us all and which we feel will really help stimulate the field.

Thank you.

ACTING CHAIRMAN GULICK: Thanks, Dr. Jolson.

TRIAL DESIGN ISSUES

ACTING CHAIRMAN GULICK: Can we turn now to begin the morning presentations, focusing on trial design issues. The first speaker will be Dr. Douglas Ward from the DuPont Circle Physicians Group, who will be speaking on a clinical perspective for challenges for experienced patients.

DR. WARD: Thank you very much.

THERAPEUTIC CHALLENGES FOR ANTIRETROVIRAL EXPERIENCED PATIENTS: A CLINICAL PERSPECTIVE

DR. WARD: The first thing I did this morning when I woke up was talk to myself a little bit to see if I had my voice back. Unfortunately, it's not. So if you close your eyes, you can just imagine you have Brenda Vaccaro talking about this for you.

My job this morning is to just go over the therapeutic challenges for heavily pretreated patients from the viewpoint of someone as a primary care treatment provider and someone who does clinical research.

I would point out that I'm going to be using the politically incorrect term of "salvage," which when I thought about this, I went back to my Merriam Webster's and found that the verb "salvage" means to rescue or save. So I think in this situation, it is an appropriate term to describe our treatment approaches for patients in these really pretreated situations.

Next slide. Defining salvage or treatment failure is a difficult subject. Certainly it can be based on failure of treatment regimens as the definition that is being used for today's meeting, failing at least two HAART regimens that have included at least one drug of each group/class.

Certainly there's a question of in that

situation: How do we define failure? Is it increasing viral load, failure to become undetectable? And certainly this is a variable answer for different patients. One of my patients who has been undetectable would certainly consider a viral load of 1,000 a failure; whereas, I have other patients who would give their eyeteeth to be at 1,000.

Alternatively, we could base salvage on other definitions, including resistance, either genotypic or phenotypic. Certainly these two definitions are very closely related. Treatment failure generally leads to resistance.

Next slide. Very briefly, one study published this year just looks at in the first, second, and third regimens there is a decrease in response rate and a decrease in sensitivity to the drugs, which explains the decreased response rate.

Next slide. Why do we need salvage therapy in this day and age with many antivirals of different classes available? For a naive patient, we really do get very good success rates. I can be very optimistic with a naive patient new to treatment that we can do a very good job of getting them undetectable and keeping them undetectable for a long time. However, there are treatment failures out there,

experienced patients, who have this failure for multiple reasons.

One of the more common I see is patients who have been on treatment for years, even over a decade now, very commonly having a prolonged history of sequential mono therapy of the RT inhibitors before a HAART became available so that they have very extensive RT resistance and when the proteases and non-nucs became available had a poor response to those because they didn't have accompanied drugs to use with them.

Another very common cause of treatment failure is noncompliance. This is a chronic problem with patients. And if a first regimen fails because of noncompliance, there is certainly a high incidence of failure of subsequent regimens for the exact same reason.

There are poor treatment choices, either from inexperienced providers or I will certainly admit and in retrospect, I made a lot of bad choices in years past simply for lack of knowledge of how to use some of our drugs. I have done things that I would never do nowadays.

And certainly there are treatment failures that we just can't explain. Nothing is black and

white in the treatment of HIV.

Next slide. How common is this problem? If you look at clinical trials, failure rates range anywhere from 5 to 60 percent. I can name trials that on treatment have 100 percent success rate and other trials even lower.

Looking at surveys of clinical practices, success rates are even lower than we see in clinical trials, where you generally have motivated, well-monitored patients.

When a first regimen fails, the success rate in subsequent regimens is even lower and makes the prognosis for further regimens even worse. And the resistance from the original regimen carries over. So you've got two failed regimens to work with on subsequent ones.

The HOBBES database that I participate in, database of about 2,500 people, Frank Pellom looked at the durability of response to subsequent regimens. Certainly the first regimen on a Kaplan-Meier curve here has significantly longer duration of response than the second or third regimens, which tend to fail more rapidly.

Next slide. Looking at the prevalence of treatment failures, I did a review of my own patient

population, which I actually for the first time found out is about 300 patients and found that 54, or 19 percent, of my patients are not on treatment. Either they haven't needed it or, for various reasons, have gone off treatment.

Twenty-six percent are undetectable, below the limit of quantification, under first HAART regimen. Seventy-seven, 27 percent, have been on treatment for a long time, became undetectable once they began a HAART regimen, and have stayed undetectable since. With 53 percent of patients undetectable on a HAART regimen, I think I'm probably a little bit above the average.

Thirty-three patients, or 12 percent, are patients who have failed multiple regimens, can be defined as someone who needed a salvage regimen and have been successful on that salvage regimen, have a prolonged undetectable viral load.

Importantly, I have 34 patients, or 12 percent of my patient population, who currently need salvage. They have been through multiple therapies. They have extensive resistance. And I don't have anything to offer them currently for an improved regimen. About four percent are in various regimens that I just couldn't assign to one of these

categories.

Next slide. Salvage treatment is obviously very difficult, which is the reason we're here today. There is a lot of cross-resistance to previously used drugs and cross-resistance of these drugs to potential new agents. So we're limited in what we can do.

Multi-drug regimens or MegaHAART, trying to use as many drugs as possible, can be difficult to take, difficult to tolerate. Traditionally, historically new agents have become available one at a time. So as with the RT inhibitors, we have successive mono therapy and then single new agents to add in to a failing regimen.

The one exception to this I can remember was around '98, when the expanded access program for three different drugs, efavirenz, abacavir, and adefovir, were all available at the same time. And certainly as clinicians, we took advantage of this for our failing patients.

In my three-physician practice, we had over 100 patients enrolled in these expanded access programs at the time trying to use multiple new agents for these salvage patients. And, indeed, a number of the patients that we had at this time we did finally

get into a successful new regimen.

Doing clinical trials in the salvage situation is also very difficult. As has been mentioned, it is a very diverse patient population, both in treatment history and resistance. And trying to draw conclusions from very different starting points is difficult.

New agent trials have generally been designed for registrational purposes and can be difficult to show efficacy in a salvage situation. So the trials are not used for this purpose.

I just did a check of the trials that my practice was offered in the last year, seeing how many trials are available for salvage. We had eight trials offered to us for treatment-naive patients. We get two or three naive patients a month. We were able to participate in some of these trials and enroll well.

We had two trials offered to us for experienced patients. However, they were very restrictive in their entry criteria; for instance, first protease failure, non-nuc-naive.

I use a lot of non-nucs. I had absolutely no one to enroll in these trials. And we did a very poor job of enrollment or simply turned the trial down because we didn't think we could enroll.

We had two trials offered to us, truly useable in a salvage situation; one of them, expanded access program with tenofovir. But, once again, by and large, simply adding in one new agent, even though it does seem to have efficacy in the setting of resistance, and one trial with interferon for HIV, simply, once again, an add-on therapy without hope of true salvage. So the trials so far don't appear to be out there for what we need looking for this.

Next slide. From the viewpoint of someone who is providing care to their patients as well as doing clinical trials, I have a number of things I want in salvage trials; first of all, a reasonable expectation that the new agent or new regimen is going to be effective and offer hope to my patient of a good response. This includes both new agents or new regimens of existing agents.

Salvage trials need to be planned and executed, even before licensing of a drug, so that we can use the agent in these trials, even before it's widely available on expanded access programs.

Patients want access to these drugs. And by the time the trials many times are done as Phase IV trials, there is already extensive experience with the drugs, making the trials difficult to enroll. Entry

criteria for trials need to be applicable to the populations that they're relevant to, not extremely restrictive, so that we have them available for the patients who need them.

The definition of success in salvage trials may not be the same as that in registrational trials. We may have different endpoints, less strict endpoints, but also we have to be flexible in how we apply these trials with bailout options for lack of efficacy in the trials.

As with all clinical trials, even in salvage, placebo controls are acceptable if the efficacy of an agent is truly unknown. And trials can also be designed to include non-drug interventions, treatment interruptions, immune stimulants, and other interventions that we may have available.

Next slide. If I can deign to approach this from the patient's viewpoint, once again, in entering a clinical trial, a patient has a reasonable expectation of efficacy of the new agent. Many of these patients who have been through many treatment regimens over the years continually failing and decreasing immune system are desperate for effective therapy. They want agents, access to new effective agents, as soon as possible because they don't have

time to wait.

Patients also are aware that using new agents as mono therapy is simply going to make the new agents less effective. And those patients who are clinically stable, despite treatment failure, are going to wait for multiple therapies used together for a more effective regimen.

In the salvage situation, we may be willing to accept more risk of toxicity if there is a possibility of success where we haven't had it before. Unfortunately, these patients after extensive treatment and frequently with advanced disease may be more prone to toxicity.

So, finally, I just want to mention to keep in mind that for the patients entering salvage trials, this isn't just an experiment. It's their treatment and their life. I think we need to keep this in mind also.

Thank you.

ACTING CHAIRMAN GULICK: Thank you, Dr. Ward.

Are there one or two questions from the panel?

(No response.)

ACTING CHAIRMAN GULICK: Must be crystal

clear. Thank you.

Our next presentation is Dr. Martin Schechter from the Canadian HIV Trials Network, who is going to talk about trial design options in adults.

OVERVIEW OF TRIAL DESIGN OPTIONS: ADULTS

DR. SCHECHTER: First of all, thank you to Dr. Jolson and the Committee for the invitation to talk today.

I'm going to try to talk about some of the challenges in dealing with trial designs and probably have to warn you that there are probably more questions than answers ahead. And if there is a laser pointer around? Ah, there is. Great.

The first question that people have approached me with is the question of whether we actually have to do randomized controls and whether in the context of salvage therapy we can look to other options.

I go back. I'll be talking a bit about the history of medicine today, the case of tuberculous meningitis. It was universally fatal prior to 1945.

In 1946, streptomycin appeared. It was a new drug in very short supply. And some treated patients were given this drug, were treated with it, and they survived. It was deemed that randomized

controls were unnecessary because the experience was so different from what historically had been observed.

The point, though, is that in this situation, we're dealing with an extremely homogeneous patient group. They all had end-stage and accurate lethal infectious disease. The outcome was mortality. The prior outcome pattern; that is, 100 percent lethality, had been fully characterized. And this was a very short-term study. Adherence was not an issue.

Now, one of the things we're dealing with is that as we move from naive populations to salvage populations in time, there is something that is rising sharply. It could be viral load. It could be other things. But, in fact, one other thing that is rising very, very sharply is patient heterogeneity in time.

What is increasing is the drug history. This is how people diverge in time through this period. The drug exposure intensity that they have experienced; genotype; phenotype; virologic status; immunologic status; clinical status; toxicities they have experienced; malabsorption; previous treatment interruptions; adherence patterns; and, finally, their attitude about treatment, which is very important. So that curve, people diverge continuously in time as we move. And, as well, unknown confounders are also

diverging.

Now, heterogeneity per se does not matter. So in and of itself, it doesn't matter if you have a heterogeneous population. It does matter when these variables are strongly prognostic.

Now, I borrowed some data from the Julio Montaner at our place from a multi-drug rescue therapy. The point here is not to look at actual data, but this is variables predicting achieving a decline below 400 in people who had multiple drug failures in the past using many, many drugs.

I just want you to look at some of the strengths of the odds ratios at predicting the ability to suppress virus in a salvage population. 3TC resistance had an odds ratio of .17, meaning that means people one-sixth as likely to achieve suppression of viral load, one-sixth as likely. That's equivalent to an odds ratio of six.

You'll see when you look at these odds ratios that they are stronger than any treatment effect we might anticipate. So, in fact, the predictor variables can be stronger than the treatment effect. And when that's true, it's very dangerous when you have heterogeneous populations.

Now, as patient heterogeneity rises in

time, there's something else falling. This could be the CD4 count, but also it's our ability to control confounders. This is plummeting in time as we move towards salvage populations.

Salvage studies, this is the previous graph of increasing heterogeneity, inability to control confounders. And this is where salvage studies live: out in this territory.

Now, can we avoid randomized trials? The attraction, obviously, when people have approached us to talk about historical controls, it's obviously a very attractive approach. And you will see, in fact, in the binder we receive numbers and numbers of case series of people, 30, 40, 50 patients trying to extrapolate what their viral load outcomes were against the observation in other groups.

There are lessons from the history of medicine; for example, gastric freezing for duodenal ulcer. The President of the American College of Surgeons decided to try cooled gastric balloons. And he did a very impressive case series.

By the way, this was in the '60s. This is not in the 1800s. He wrote, "Since 1961, no patients with duodenal ulcer referred for elective operation have been operated on in the senior author's service.

This circumstance itself bespeaks the confidence in the method by patients as well as surgeons."

Well, this led to the sale of 2,500 gastric freeze balloons. An estimated 15,000 patients were chilled. Finally, a double-blind randomized control trial was done in the '60s. The outcomes were poor outcomes: Surgery, bleed, or intractable pain. They did a sham procedure. Their rate was 44 percent. In the freeze group, they had a higher rate of poor outcomes when it was done as a randomized trial.

There is a VA study of estrogen in the treatment of prostate cancer. This is an RCT of 2,300 patients recruited over 7 years, no change in the eligibility criteria throughout the trial. When you look at what happens to placebo patients in the first two and a half years, they had worse survival than the estrogen patients in the last 2.5. So someone could very easily come along, take this as a series, use these patients as historical controls, and conclude that estrogen was effective when, in fact, in the trial overall, there was no treatment effect.

In uncontrolled Phase II cancer studies in advanced bowel cancer in 20 different case series of rapid injection 5-FU, when you look at the 6 largest series, 40 to 150, the response rates ranged from 11

percent to 55 percent.

So this author could use this author as control and note a treatment effect of fivefold. These numbers are kind of the range of things you see in the literature about ability to achieve a plasma viral load suppression.

So traditional orthodoxy is that it is well-known that historical control studies are far more likely to yield positive results. There are a number of articles in the literature that show this. And that has led to the dominance of the randomized control trial.

There continues to be an ongoing debate. And just to show you a paper published this year in the *New England Journal*, I know you can't see this, but let me just try to tell you there are five treatment conditions here. And on each of these, these are the odds ratios of treatment effect. The closed circles are the results from randomized trials. The open circles are the results from case control or cohort studies.

You can see that, in fact, well-done observational studies don't do too badly. I think this is here to show you the range that you can get from different clinical trials, that the observational

studies do pretty well at mimicking the treatment effect that you see in some of the RCTs. This was in the *New England Journal* this year, Concato, Shaha and Horwitz, the point being that those were well-designed case control and cohort studies.

And those are not the same as historical control studies or chart reviews. These involve the careful selection of controls. They're usually concurrent. But they could play a role in a situation where prognostic variables are completely categorized.

Now, what about the idea of using non-randomized concurrent comparisons by post-randomization variables? That's a mouthful, but what's an example? When you do a within-study comparison based on adherence to a regimen, a very attractive alternative, for example, within the context of the trial, if people who adhere to the drug do better, doesn't that prove that the drug is effective than people who don't adhere as well?

So we go to the history of medicine again, and we look at a lipid-lowering trial. This is people in one arm of a study who were given a medication called medication A. These are people who adhered, less than 80 percent. By pill count, these are the people who adhere, greater than 80 percent.

There are the numbers. You can see the mortality rate was double in the people who did not adhere than the people who adhered. This, by the way, was adjusted for 40 baseline predictors, so everything you can think of, the things that we would think of in HIV, they have thought of for cardiovascular mortality: blood pressure, prior MI, New York clarification, angina, and so on. So quite a clear effect that if you take this drug, you do twice as well as if you don't take it and, in fact, turns out that this was the placebo arm of the trial. In fact, this table looks identical to the table you got in the active arm.

So what does this mean? Does placebo work better or does it tell us that people who adhere are destined to do better because they adhere? It reminds us that there are more confounders on heaven and Earth that are dreamt of in our philosophy.

Salvage therapy and non-randomized controls. As I said, we are dealing with very heterogeneous populations, some variables measurable, some not.

We have some very strong prognostic factors, many as yet identified: variable, surrogate marker, outcomes. So I think we have to deal very

cautiously, particularly in this population.

Now, it could be that if we were to move the definition of salvage therapy further along the natural history to where it became homogeneous again, we might do better. So if we can move later and we define people by being in worse categories right across the board and getting closer to what might we use the word "salvage" really for, we can possibly get to a situation where outcomes are well-characterized and where this is possible.

However, in the meantime, how do we control confounders? We have randomization. We have large sample size. And when you have the combination therapy of these two things, randomization, large sample size, you can get a likely result that you can distribute known and unknown confounders equally.

Now, if you look, for example, in the package we were sent, you will see a few papers with very large sample sizes, but you will also see a whole number of case series involving 18, 20, 13, 25, 40 patients.

What are the remedies for confounding and smaller sample size studies? Well, we can stratify the randomization, which means you pick your strongest prognostic factors.

You stratify first and then you randomize. If there are *n* such variables, you will have 2^n strata. And this becomes unwieldy. Sometimes people will build a risk index combining different variables and stratify based on that.

There are schemes in which you have an adaptive allocation, which minimizes the imbalances between the groups. So as you go along, if you see that you have an imbalance with regard to some prognostic factor, you would adjust the randomization to try to address that. So that is an adaptive allocation.

And, also, there is always post hoc adjustment. Now, the worry with post hoc adjustment by multi-variate analysis is the debate about whether you are having an effect on unknown confounders. And there is the issue of what happens when your crude result is different from your multi-variate result.

Again, let me just state something that we all know. There is no within-study remedy for lack of power in small sample size studies. You see these small case series of 18 and 20 and 25 patients. So this is worth remembering when we see that.

The issue of blinding is an interesting one in the context of salvage. It's orthodoxy, of

course, that blinding is required in trials. There are numerous studies that have shown that less bias occurs when you have fully blinded studies and you have a far more likelihood of positive results.

For example, this is a large series, a meta analysis, published in JAMA in 1995, 33 meta analyses, 250 trials involving 52,000 participants, 12,000 outcome events.

This is what they call blinding. They called it "allocation concealment." "Adequate" meant the ideal. "Unclear" was sort of a middle category. And "inadequate" would be sort of an unblinded randomization.

These are the odds ratio, one being referent for adequate. You can see that as you move down to less and less blinding, you get stronger and stronger treatment effects. There are a number of papers in the literature that show this to be the case.

However, one shouldn't get too strident. Is blinding feasible, for example, in the context of salvage therapy? That's obviously an important question for multi-drug studies. And can the artifact of blinding introduce more bias than it prevents?

For example, in a study that we are

looking at in which we are going to compare standard therapy, less than four drugs, versus MegaHAART, if you look at the issue of blinding, you first think about that standard therapy may benefit by greater adherence. That's how if it were to become more efficacious in the result it may do so simply because adherence is better.

If we were to try to blind this study, we would, first of all, need from 9 to 17 different types of pills. And, more importantly, we would put on the standard therapy arm an artificial pill burden that would not be experienced in real life under real life standard HAART. So, in fact, this bias, this artifact in the clinical trial, the blinding, could wipe out the adherence advantage and introduce a virus.

Another problem as we move through naive to salvage is that intent to treat and treatment received diverge during this time period. This raises particular clinical trial challenges, rapid crossover and dropout.

For example, if you, say, cease in a study, you are actually moving from multi-drug to an interruption arm. Intent to treat becomes meaningless. Treatment received becomes highly biased.

The availability of new treatments or strategies as you move forward in time, genotypic testing, compassion, and access are dangerous when they are not built or accommodated into the protocol.

Now, if we deal with some of these, offer of early versus late therapy may induce better protocol adherence to keep people in the arm to which they are allocated.

For example, if we are doing an interruption trial, we may do interruption now versus interruption in X months from now. And participant education is very important to keep treatment received. And the possibility of a switch after a poor response triggering a crossover is also a way to try to maximize that.

The availability of new treatments or strategies, we need obviously to think about rolling protocols that can roll with the punches and preplan future randomizations of future options.

Let me speak briefly about factorial designs and give you an illustration. One could ask a question. In people who were treated with indinavir who are NNRTI-naive and who we would like to try different strategies, you could try a simple randomized trial of saquinavir, ritonavir,

delavirdine, versus nelfinavir, and adefovir, which will answer one question but obviously leave a number of questions unanswered after that trial was done.

Well, an alternative way to approach this -- and here is the question again: What is the role of adefovir, delavirdine in these kinds of patients? What about approaching it this way, which is what was done in ACTG 359, is to say there are three options in this axis, delavirdine, adefovir, or combination of both, and in this axis ritonavir or nelfinavir all in a base of saquinavir? We randomized approximately 50 people to each of these 6 arms.

What do you get out of this? Well, you get a lot of things because you have 100 patients on delavirdine, 100 on adefovir, 100 on the combination. That gives you the comparisons in the vertical axis.

In the horizontal access, you have about 150 patients randomized to ritonavir and nelfinavir. So you're answering a number of questions. And, even better, if there are any interactions, for example, between two drugs, -- and I don't mean drug interactions; I mean treatment effect interactions -- you will be able to discern these within this context.

We are currently looking at a study where, instead of looking at combinations of drugs, we are

looking at combinations of strategies. Optima is a two-by-two factorial which involves a treatment interruption, no interruption, MiniHAART versus MegaHAART.

And it will be a two-by-two factorial design, which will allow the study of the effect of the interruption, the study of the effect of mini versus mega, and possibly the fact that these two strategies might interact and lead to some kind of synergy.

Here is another one, which is a trial of HIV-infected women in Tanzania in the *Lancet*, 1998. This was to test general vitamins, Vitamin A, whether their combination worked versus double placebo. So you could have one vitamin, both vitamins, or nothing. In fact, this showed that I believe the multivitamins were effective and the Vitamin A was not.

Interestingly, when I did a Medline search and I used the term "factorial design" as a keyword anywhere in the text and I cross-referenced that with HIV, I actually found three references, which struck me as very low, but that's what I got. I think it's safe to say that factorial designs are woefully under-utilized in the medical literature in general.

Now, the variables that we use in a

factorial design can be the combination. So here, for example, is a two-by-two factorial study, where there are four different combinations. And that looks like the little two-by-two table I just showed you. So that's one two-by-two factorial.

Now, rather than randomizing on another variable, we might have a stratification. This might be a genotypic resistance, and this might be its absence. What we do is stratify and send each group to their two-by-two factorial trial. So the same four combinations are used.

Now, not only do you get the Combo 1 versus Combo 2 comparisons in the presence or absence of these, but you get the vertical comparisons. And you can look at the interaction of these treatment effects with whether the factor is present or absent.

Now, suppose we have a complex situation, we have one factor, like a mutation which has three straight up. We have another factor which has three straight up. And we have three combinations of drugs we want to compare, one, two, and three.

You can see if we were to do a full factorial design, we would be talking about 27 different cells. And it becomes quite unwieldy. So we can turn to something called the Latin Square

design. This is something that is used in basic science, in pharmacokinetic studies, and very commonly in veterinary science.

A Medline search using the term "Latin Square" as a text word with the cross-reference to HIV revealed no hits. So I haven't seen this done, but there is a very good article in 1998 JID which talks about the efficiencies of this.

In this case, rather than doing 27 cells, which would be the full factorial, you build a three-by-three table. A, B, C is this variable, I, II, III here. And, rather than trying to offer I, II, III in each cell, you move across like this.

So every vertical row has each of the combinations present. Every horizontal row has each of the combinations present. There are efficiencies here in the comparisons you can make. It's obviously not as robust as the full factorial design, but it's also one-third as large.

So factorial designs are ideally suited when you have multiple therapies that exist and we can give them in different combinations. They're ideally suited when you have different strategies that can be combined. So you might be looking at drug combinations against interruptions, drug combinations

against vaccines or immunomodulators or adjunctive therapies or complementary therapies. There are ideal scenarios for setting up factorial designs that involve each of these or two of them at a time.

You can look at independent treatment effects within the design, and you can also look for synergies of different combinations. These are symmetric, and they're highly efficient. Again, if you look at several publications; for example, the JID publication will show you the power curves that tell you the efficiencies and the fact that you do receive much more bang for your buck when you go this route.

Again, as I mentioned earlier, they're woefully under-utilized in the clinical trial literature, particularly in HIV, where we don't see them all that often.

Now let me conclude by looking at an issue which is not easy to solve, but it is one that we are left with, which is the issue of drug-wise versus strategy-wise evaluation. I will deal with this hypothetically.

Suppose we have new drugs A and B in two different classes and we're hopeful because they appear to have new resistance patterns within their class and A is available for trials now and B is going

to be available in six months, say. Well, what might happen?

Well, you can see in the drug-wise evaluation, first somebody will do a trial of A and then later, six months later, a trial of B will begin, switch B versus non-switch.

Now, each of these trials will probably contaminate the other because people in the first trial will want access to B and vice versa. So what you end up with is two not mono therapy trials but switch of mono therapy with possible co-intervention in each trial. And the picture looks like this, where you get two independent questions possibly answered but with contamination. That would be the drug-wise approach.

Now, what if we were able somehow to take a strategy-wise approach to this evaluation? We could start trial one of switch A versus non-switch. We preschedule a second randomization of switch B versus non-switch when B is available. This is a two-by-two factorial design. And the trial would look like this. Okay? So that's a two-by-two factorial.

Another way we could approach strategy-wise drug evaluation would be to wait and say, "Let's wait six months. And let's actually do

the double switch" because if that's the clinically relevant question, let's do it that way. And we perform a two-by-two factorial double switch with double the sample size and look at the interactive effect. So that trial would look like that. You get AB and combination AB from the outset if you were to wait.

Miscellaneous considerations: randomized consent designs or Zelen designs, which is where if the two arms in the study are much less or wildly different from one another.

The classic example where this was used is in the lumpectomy versus mastectomy trial. And, rather than asking women to submit themselves to a randomization, where they were depending on the flip of a coin to determine what kind of surgery they got, they actually randomized first and then sought consent. This sometimes works in trials where there is a marked difference between the treatment arms.

There is an -- now, this is a very controversial subject -- adaptive assignment, so-called play the winner. You have to be in a situation where you have rapid endpoints, you are always seeing what is going on in the trial. But there have been classic examples where this has failed

miserably. And it violates the simple rapid objective foolproof thing we would like in treatment assignment.

Finally, I will just end quickly with a little talk about things besides -- this really is a bad title. It should be "Other Endpoints." Quality of life, economic costs and savings, survival, quality-adjusted life years, and cost per quality. These are issues I think that have to be addressed in salvage trials particularly, rather than simply looking at surrogate marker endpoints.

Just some comparators. There is a list of U.S. dollars per quality of life year gained, various different types of procedures. Where I come from, we have to show when we introduce a new thing into our formulary, where it fits in onto the table and can be justified.

So I will stop there. Thank you very much.

ACTING CHAIRMAN GULICK: Thanks, Dr. Schechter.

(Applause.)

ACTING CHAIRMAN GULICK: Are there one or two quick questions? Dr. Wong?

DR. WONG: I didn't understand the Latin Square design. Could you just expand a little, maybe

show an example of how that might be done?

DR. SCHECHTER: Well, actually, it comes from agriculture and from different sciences. I wish I could get that table back. If you had three different combinations and you had -- I think the example in the JID paper looks at -- let's see if -- well, anyway, imagine a three-by-three table and you have -- let's say across the top, the categorization is three different mutation patterns and vertically, say, numbers of protease mutations.

If you wanted to assign each of the three combinations you were looking at to each of those nine combinations of mutation and resistance patterns, you would require 27 different allocations.

But if you do it by going one, two, three, then two, three, one, then three, two, one, rather than needing 27 different cells, you need 9 cells because every vertical column will have all 3 combinations in it and every row will have all 3 combinations.

So you will be able to look at the three combinations in the context of each of the three mutation patterns. and each of the three other factors that you're looking at. But you do not get the full robust number of comparisons that you can make with a

factorial.

ACTING CHAIRMAN GULICK: Dr. Mellors?

DR. MELLORS: Martin, factorial design is appealing for many of the reasons you outlined, but one of the issues always becomes that you can be powered to assess differences across the factors but not between the individual cells and that what happens is you get underpowered cells that may be of particular interest. And when you power those cells for inter-cell comparisons, your sample size becomes enormous.

DR. SCHECHTER: Yes, that's an issue. I guess the thing to say about factorial designs is that if you were to have one burning clinical question and have 300 patients to answer it with, probably you would not want to dilute that through a factorial design.

So the efficiencies of factorial design only can be fully gained if you're willing to go up marginally in sample size because if you have 300 patients, you might be able to answer 3 questions with them, rather than one.

So I don't want to deceive anyone that with the same number of patients by using a factorial design, you achieve the same amount of power on the

within-self comparisons. That's not true.

But if you were willing to increase your sample size overall or go multi-center, you can with an increase in the number of patients answer far more questions than you could if those patients were distributed among three different questions at three different places.

ACTING CHAIRMAN GULICK: Okay. Thanks again.

Our next speaker is Dr. Coleen Cunningham from SUNY Upstate, who will be talking about trial design options in pediatrics.

OVERVIEW OF TRIAL DESIGN OPTIONS: PEDIATRICS

DR. CUNNINGHAM: Thank you for the invitation to speak here today. I have a very difficult task following that excellent presentation, and I hope I manage it well.

I just want to say that I was told my main job here was when discussions get around to trial designs and proposed studies that just every five or ten minutes, I'm just supposed to say, "Then don't forget the child." So that part of the job I will have no trouble with.

And I hope that in these few minutes I can give you -- I won't wander away from it -- some of the

issues related to pediatrics that I was asked to cover.

Before I forget, I also want to thank Steve Spector and Tory Rendon from the PACTG, who gave me some updated information about actual numbers that are available at clinical trial sites. So when we talk about pediatric numbers, I have some hard data.

The three bullets that I was asked to cover today were to talk about: the epidemiology of treatment experience in pediatrics; how does the smaller number of HIV-infected children, as compared to adults, impact on trial designs that are feasible; and how does management of HIV disease in children impact the type of trial design options, as compared to adults. I will try to cover each of those three areas quickly.

So, first of all, to talk a little bit about the epidemiology of treatment experience in children. I can't tell you nationwide exactly how many children have received what combination, but I can tell you that the vast majority of HIV-infected children are multi-drug-experienced.

And because of the evolution of drug availability in this country, the majority, or at least a large number of kids who are infected were

exposed to sequential mono, dual therapy and then combination therapy, or at least dual combination, then triple combination.

There really are three major factors I think that account for or that explain why our current population of children has the treatment experience that they do.

First of all is the evolution of treatment. Second of all is, although that evolution of treatment may not be optimal compared to what we do today, it did allow for increase in survival of children who were alive and ill with their HIV disease in the '90s. We now have significantly decreased mortality, and many children are living longer and, therefore, exposed to more drugs over that time period.

Finally, we had the fortunate experience of having relatively few newly infected infants. As I will show you, there really is a limited number of newly infected young infants, not to say there is none but the numbers of young children who are treatment-naive is becoming smaller all the time. And so we have a sort of pool of kids or population of kids who are growing older and seeing more and more drugs.

Next slide, please. So first I want to cover the evolution of treatment in pediatrics.

You can go to the next slide. As most of you also have experienced, treatment evolved over the '90s. In the early '90s, we were often using AZT mono therapy because that is all we had. We then went to combinations including AZT/ddI, AZT/3TC. The first PI that was extensively used in pediatrics was ritonavir. And the three-drug regimens really came into relatively common use around '97.

Next slide. I just want to show you some data from PACTG 219, which is a long-term follow-up study, of children. Previously to be enrolled in this trial you had to be a child in another PACTG study. And then you went on to 219, which included follow-up to age 21.

So there is some bias in that if you were enrolled in this trial at this time point, you had to have been on some study and, therefore, probably were more likely to be treated than the kids that didn't go on this study.

However, this is follow-up data on children that were enrolled into that study, HIV-infected children that were enrolled onto that study, prior to January 1st, 1996. And as you can

see, in 1995 there was virtually no PI use. By 1997, 30 percent of the children were on some PI. And in 1999, over 70 percent of the children were on some PI.

Certainly kids have been on triple combinations and MegaHAART therapy. Unfortunately, many of the kids had some experience to nucs prior to going on the triple combinations. And so the success rate of treatments has not always been optimal.

Next slide, please. This evolution of treatment has led to a decreased mortality. More of the infected children are surviving for years.

Next slide. From the same study and the same cohort of infected children that were enrolled prior to 1995, as you see, over time mortality in 1996 -- and this is percent per year. I'm sorry. When my slide converted to this, some of the things got omitted. But you can see the mortality is less than one percent in 1999.

Next slide. That mortality decrease occurred across all racial and ethnic groups.

Next slide. And it also occurred across age groups. The yellow bars are the youngest age group, the two to six-year-olds. The blue bars, not a good choice of colors, but the 6 to 13-year-olds, also declines. And the over 13-year-olds declined not

quite as much. Many of those children have been infected for a long time.

Next slide. Finally, data that shows the relatively limited pool of newly infected kids. And, again, this is a slide that didn't quite convert right, but prior to 1993, historically the transmission rate in this country is roughly 25 percent.

And that is what it was on the placebo arm of PACTG 076. The HIV transmission from mother to baby was eight percent in AZT mono therapy, as shown in 076.

PACTG 185, the transmission rate in both arms was 4.8 percent. And the results of 316 are not officially available, but we do know that the transmission rate was significantly less than the 5 percent hypothesized for the study. So I put three percent in there. But we know that the transmission rate is continuing to decline in this country.

Next slide. So, to wrap up the epidemiology part of the discussion, children with HIV in this country are primarily treatment-experienced, often multiple class-experienced, and may need also sequential mono and dual nucleoside therapy.

Exploring options for the

treatment-experienced children is critically important for these children in order to provide care for these children. We really have to evaluate treatment options, management strategies, and effectiveness of every new agent in this population.

Now to talk a little bit about how many infected children are there and whether or not that would impact on trial design and are these children potentially available to participate in clinical trials and what age groups are available. And I just want to show you some data from PACTG. This was collected within the last month. So it's quite current.

As most of you know, the Pediatric AIDS Clinical Trials Group is made up of two separate subgroups that really function as one working entity. The NICHD tends to represent the smaller sites and has 28 relatively small sites. Those sites report that they care for a total of 2,671 infected children. Of that total, 413 are new children; that is, new, infected children that presented within the last year, and 1,213 are adolescents.

Among the NIAID sites, there are 23 sites that care for 5,800 infected children, 736 new, and 1,738 adolescents; so overall, over 8,000 infected

children who are currently in care at PACTG sites.

Next slide. The racial and ethnic breakdowns of the children are available. I just want to point out in the infant category here, the zero to 23-month, the vast majority of these children are babies born to HIV-infected mothers. Very few of them will end up being HIV-infected; so would not obviously be available for treatment trials.

Next slide. How do the numbers impact on trial design options? I think that there is a very, very limited ability to do pediatric studies in treatment-naive children.

Any studies that could be done in that population would be very small focused and really targeted to ask very specific questions. However, I do think that the number of experienced children is much greater.

And, really, a number of efficacy studies could be done, particularly if endpoints were virologic and not clinical. We definitely need pharmacokinetic safety and activity data, and we have the numbers of children to be able to collect that data.

Next slide. I just want to spend one minute talking about some of the treatment issues that

are unique to pediatrics. Why do we even need to do these studies in children? Why can't we just take what you learn from adults and go on our merry way, take care of the children? Because there are a number of things about children that I can't just take your data and use it.

First of all, I don't know the dose to use. You cannot predict pediatric dosing based on adult pharmacokinetics. Really, I don't just have to answer the pharmacokinetics for sort of the generic adult. I have to know the dosing, the appropriate dose, for a 2 and a half-kilo 4-week-old and the appropriate dose for a 100-kilo 14-year-old. It's a huge range. The dose and a number of pharmacokinetic parameters will vary greatly across that range.

Dosing the volume, palatability. I don't mean to pick on one particular PI, but all the PIs taste terrible. And I just want to ask you if you have all tasted some of the liquid PIs.

Imagine giving a large volume of liquid ritonavir to a child several times a day. It's a huge issue. I actually want to point out that that's a reason that the placebo comparators really just can't be done in these pediatric trials with a liquid preparation.

The frequency issues. We have to fit things into school schedules. Toxicities may be different in children. I think, fortunately, my general experience is things have been better tolerated in children. At least they don't complain quite as much as adults do.

Certainly long-term toxicities, the lipid abnormalities and the mitochondrial toxicities, those exposures over years may be very different in a child than they are in an adult.

I think I'm almost done. Just some other issues that are somewhat different. Pretty much all the children are dependent on an adult to have the medicine delivered. And that may lead to better adherence. It may lead to worse adherence. That's obviously going to be different than what you see in adults.

Children have frequent minor viral illnesses, the common viral crud, as I like to call it. These are illnesses that every child gets but may lead to a couple of days of vomiting or a couple of days of inability to eat. And those kinds of treatment interruptions are incredibly common in pediatrics and may affect drug usage. Children are exposed to a number of other antibiotics and

medications on a relatively frequent basis.

And some general comments. Just viral load set points and CD4 counts, both are generally much higher in pediatrics and make patient selection and trial design issues a little bit different in children as well.

In summary, I really want to remind people that pediatric trials really must run concurrently with adult trials. When you have decided that a drug works in adults, we can't then just start from scratch doing the evaluations of treatment in children. That will put the children's treatment a couple of years behind adult treatment, and that's not appropriate.

We must have pediatric formulations available for all drugs. The PK and tolerability, which clearly includes palatability, and safety data must be available. We need to understand long-term safety. And we do need to evaluate different management strategies.

The last slide is just a plug that, really, the majority of the trials carried out, actually, in the U.S. have been within the Pediatric AIDS Clinical Trials Group. And there really is a large number of children currently in care at those sites. A number of trials could be done and really

must be done to address many of these issues for children.

So thank you.

ACTING CHAIRMAN GULICK: Thanks, Dr. Cunningham.

(Applause.)

ACTING CHAIRMAN GULICK: Are there one or two burning questions for Dr. Cunningham?

(No response.)

ACTING CHAIRMAN GULICK: Okay. Thank you.

Next is Mr. Carlton Hogan from the CPCRA and the University of Minnesota School for Public Health to present a patient perspective on salvage trial design.

TRIAL DESIGN OPTIONS: PATIENT PERSPECTIVE

MR. HOGAN: Good morning to the Committee and to everyone else. Thanks for having me here. I am a member of a group called the Coalition for Salvage Therapy. And a great deal of what I say is going to represent positions of that group in those areas where perhaps my personal opinions may differ a little bit or areas where we have not accurately discussed, I'll do my best to clarify so that the two agendas don't get mixed together.

There is a definitional problem in what is

a true salvage patient. We have seen a number of ad hoc definitions of salvage. I say "ad hoc" because they sort of have appeared in eligibility criteria, have not been formalized in any sense.

Some of these we would not consider salvage patients, NNRTI-naive, experienced with only two protease. These are clearly patients who have exhausted some of the armamentarium, but it would be premature to say they have exhausted all of the armamentarium.

What we provisionally use as a definition of a salvage patient within the Coalition of Salvage Therapy is a person who cannot achieve an adequate virological response given the existing agents.

And it is our very strong and heartfelt conviction that, as difficult a group as this is, as unlikely as it is to see a response in this group, as challenging as this is for regulatory trials, this is our number one priority in HIV therapeutics right now.

A lot of us who were able to control the virus to some degree using existing therapies have some coast time. There are people who do not. And so for the purpose of Coalition of Salvage Therapy, we are focusing on persons who have no conventional treatments left available to them.

Next slide, please. Just to talk a little bit about the Coalition of Salvage Therapy, it's an ad hoc coalition. I think it is safe to say we have members of all the major AIDS activist groups involved. As I said, we focus on patients with few or no viable options.

One of our biggest interests and where we have expended a lot of effort is to facilitate inter-sponsor collaborative research. I'm happy to say that to a very substantial degree, industry has been very responsive and has really been willing to try some new things to challenge themselves to rewrite the play book.

So we really appreciate that and offer our thanks to those companies that have been willing to entertain these ideas. We feel it's incredibly important that for persons who have no options and who may or may not be eligible for current trials, that there be some form of a limited expanded access.

We're not talking ddI expanded access with 20,000 patients. We're talking about very limited expanded access simply for those people who really need a new option now. We feel that this is an important consideration. We would like to see it occurring earlier than it has been recently.

The last few drugs which have had expanded accesses, we have seen expanded accesses open up very, very shortly before registration. We feel that while that might be within the letter of expanded access, it's not within the spirit. And we would like to see earlier access to these therapeutics for patients who have no other options.

Next slide. We're uncomfortable with studies that involve patients, salvage patients, as we have defined them being on mono therapy or what we call virtual mono therapy for any substantial duration. By "virtual mono therapy," we mean merely adding one new agent to an already failing background therapy.

We do understand the scientific issues involved. We understand the need to get clean PK and pharmacodynamic data, to get initial indications of activity before we look at efficacy.

These are not issues which we blithely dispose of. However, we feel very, very strongly that where these studies need to be done, patients need to be exposed to those agents as mono therapy or virtual mono therapy for as short a period as possible.

Some of this has come under the rubric of intensification trials. Again, this is a term that is

poorly defined, and I think you would get probably half a dozen definitions of what an intensification trial is if you asked half a dozen people in this room.

By "intensification trial," we mean exactly what we were talking about about mono therapy, merely throwing a new drug on top of a failing regimen.

Beyond the concerns which we have already said, there is certainly inherent futility in this approach. What are you going to keep doing: add a drug, wait until it fails, add another?

I mean, we already have people on eight or nine drugs. We are getting to the point where it is possible that we are going to end up killing them off of therapy before they actually get a virological response.

So, I mean, it's *reductiu ad absurdum*, but it is important to realize that intensification as a primary principle of therapy is inherently futile.

Next slide. These are issues which I have already touched on a little bit. We would like to see some of the pharmacodynamic stuff done in HIV-negative patients if it's possible. We understand the drug interaction stuff probably cannot be, but wherever

possible, persons in earlier stages of disease, patients who are HIV-negative, it would be very nice to see as much of that research as is scientifically feasible be done on those populations.

This may be overly optimistic, but we have got people who are willing to enroll in research studies and enroll in PK or pharmacodynamic studies which are among the most intensive designs in terms of patient involvement, in terms of what you are asking from the patient.

So this is a population that clearly is eager and willing to be research participants. And they offer opportunity to look at the persons who first got on the drug. If these people are maintained on drugs, they will have the longest exposure of anybody out there. So, wherever possible, we would like to see longer-term follow-up with those studies.

I need to sort of bracket that point and say this is perhaps -- I can't speak to whether that's the coalition's position or not because we haven't actually discussed that exact, specific issue, to my knowledge.

Next slide. Concentration-controlled trials. Well, it's obvious to everybody in the room that there are a staggering number of determinants of

successful therapy. Just in the past couple of years, we have become aware of the importance of things like cytochrome p450.

Protein-binding, of course, has sunk I don't know how many protease inhibitor candidates. Just recently, there is a growing interest in p-2 glycoprotein. And we feel that this may be a very significant area in relation to toxicity. So we would like to see more research in there.

Impaired gastrointestinal function certainly in later-stage patients may be a very important determinant of therapy. There are differences between intracellular and extracellular concentrations. Very important to us, very, very important to us, is the effect of hepatitis and other comorbidities on drug absorption and retention and other perhaps unknown drug and food interactions than those that are listed above.

Next slide. So in regards to these type of studies, some of the questions that we feel that are important, need to be looked at are: What are the implications of transient dips below therapeutic levels?

We have seen dosing schemes of some drugs in the past few years where there are brief periods

during the day where, in some patients at least, the drug does drop below what would be considered an adequate therapeutic level. How important is that? How long a duration can that be tolerated for? How significant is that? It's just something where there is no clarity on.

I think everybody feels a concern about it, but I personally am unaware of very much research that really looks directly at that issue. Of course, the big issue this year is: Can resistance be overcome by increased drug concentration? It seems like fairly soon Baskin Robbins is going to be offering ritonavir ice cream the way it is being added to every possible combination out there.

Whether simply increasing drug concentration can overcome resistance is probably a very nuance question and very drug-dependent. And, again, this may perhaps represent my concerns a little bit more than the coalition's.

I have real concerns about blockading p450 for four, five, six, seven years. We have no idea what the effects are of doing that. Over the history of evolution, plants have sort of developed various things to keep us from being limp. We developed more sophisticated livers to be able to process this stuff.

And there is a reason for those liver enzymes.

I personally believe that blockading p450 may even open up the possibility to toxicities from some foods. Now, that's sheer speculation, of course, but it illustrates the fact that we really just don't know what this means.

Of course, when you add in the concomitant medications, we have already seen the enormous complications of balancing drug levels in people having to get therapeutic drug monitoring to adjust some of their concomitant medications in the presence of ritonavir or other potent inhibitors.

Next slide. There is probably more research into this, but we would like to see it even more clarified. What is the variance between individuals, not only in drug concentrations at particular points in time but sort of over the day of the dynamics? Of course, all of the other factors, like concomitant medications, will impact that to a substantial degree.

Is it the case that there is a point of balance between simplicity of dosing and adequate or over-adequate drug levels? I mean, is there some sort of trade-off where maybe one-state dosing will improve adherence to the point where it may overcome the fact

that there are transient dips in level?

This is an open question. We don't know, but there is clearly going to be some balance between adherence and drug concentration as we get to these simpler and simpler regimens that are taken less and less frequently.

This next point, to my knowledge, we have not discussed in the Coalition for Salvage Therapy, but it's a great issue of mine. Do what degree are we seeing host resistance? For people who have been on nucleosides, for example, for a decade now potentially, what is happening to their ability to phosphorylate nucleoside enzymes? There will probably be other host resistance phenomena that will crop up as we study these drugs over longer and longer periods of time.

Clearly there are new equilibriums established in terms of having action. Does that, in fact, raise the risk of some host resistance phenomena as well? Of course, inducer drugs, drugs that induce p450 cytochrome, will complicate this issue even more.

We're now looking at the option of some treatments that simply cannot be administered orally. How much is compliance going to differ from oral compounds? What is going to be the virological impact

of that difference in compliance?

It's our sense that for patients who are truly in a salvage position where they really cannot get their viral load down, that they are more likely to be highly compliant with injection regimens. This is speculation, of course, but we feel like people who are aware that this may be their last chance are going to be a little bit more careful. In less severe populations, we are very curious to see how treatments will be accepted that are not administered orally.

Next slide. There are some real priorities out there. At the moment, perhaps the salvage population to the research community, to industry, to patient groups is sort of a niche group or a minority group. We fear this may not be the case indefinitely.

We have now seen documentation of drugs resistant to each of the three classes separately and transmission of drugs resistant to all three classes. Of course, there is an artifact of survival, not that I'm speaking out against survival, but the fat is the longer you survive, the longer you are on drugs and have an opportunity to acquire resistance.

So the group of patients that are highly resistant to therapies we believe is going to grow and

become a very substantial proportion of patients who are being treated.

Next slide, please. This gets back to our definition of salvage. We have seen some studies recently that are important to salvage trials that we feel really are not salvage trials. We are glad these trials occurred. They were important trials. But they don't address the group of our greatest interest.

Parenthetically, I mean, we do understand the reservations. We do understand the difficulty of seeing a response, the enormous number of confounding factors in salvage populations. We're not blithely rushing that stuff aside.

But, again, our priority is persons who are at imminent risk of serious illness or death. And we're not going to back away from that. So we're going to work with you to figure out solutions to those very real problems, which we're not just brushing them aside. We understand they are there.

Next slide. It is our strong contention that any enzymes that offer only one novel agent are very unlikely to succeed. The great risk there is suppose you have salvage agent A available today and salvage agent B available in six months. Patients starting A now may end up ruining their chance of

getting a very powerful response from the combination of A and B. So, wherever possible, we would like to see more than one novel agent be used at a time in salvage populations.

Again, we are going to talk a little bit about the design issues in a moment. We are not being pie in the sky in saying this is easy and you guys should just be giving us drugs and drugs in the bodies.

We understand there are safety issues around this. However, it is really not in patients' interest to acquire resistance to new therapies before they can be used in adequate combinations.

It has never been easy to coordinate trials with multiple sponsors, but in the last year, there has really been a sea change. We really have to offer a lot of credit to companies like Abbott, Gilead, Trimeris that have been willing to talk to us about these issues, have been willing to entertain the idea of overlapping expanded accesses, possibly salvage trials from more than one experimental agent.

But, you know, we understand these companies are businesses. Their primary goal is registration. So what we absolutely need -- and if there is one key point I think the Coalition for

Salvage Therapy would like to bring forward at this meeting, we need strong guidance from the agency to industry about how if it is possible to use multiple experimental agents in a registrational trial and what the parameters of that are.

We want everybody to know what the rule book is and so the industry can go into these trials and know to what degree they can put this trial into the registrational packet and have it serve their ends as well because the drug companies are not charities. They're in to get their drugs approved. And they need guidance on how to do this sort of work and still achieve their goals.

So our message to you folks at FDA is you really need to come up with some very clear-cut rules and make industry aware of those rules and sort of give a very clear view of the playing field.

Next slide. Background therapy in salvage trials is really a challenge. The heterogeneity of previous treatment regimens makes it just about impossible to come up with a background therapy. I doubt you could find any two patients with identical treatment histories in every a very large HIV clinic.

We feel that background therapy needs to be flexible. And we would like to see it individually

optimized using phenotypic and genotypic resistance.

There are some confounding issues here. However, in properly randomized trials that are adequately powered, we think that this is achievable.

And preservation of future treatment options vis-a-vis later combinations should always be a strong consideration. And it might even be a useful endpoint for some of these trials to look at the end of the trial at what the resistance profiles are and whether one drug may have offered a clinical benefit; yet, impacted the future course of treatment by increasing resistance.

We think it is very important, and we urge that it be considered as a secondary endpoint in trials to look at resistance at the end of the trial.

Next slide. Assuming we get several sponsors to support a salvage trial, we would like to see that trial produce the most information. We would like to optimize it and milk it for what it's worth.

In the case of two experimental drugs, such a study might look like background therapy versus drug A plus background therapy versus drug B plus background therapy plus A plus B. This is a classic factorial design on top of optimized background therapy.

I need to insert the note that some of my colleagues are uncomfortable with this and are uncomfortable with the optimized background therapy arm. So there is not a clear consensus on this.

But this is a true factorial on top of background therapy. And it will allow us to assess not only the relative contributions of A and B on top of background therapy comparing them to each other but also comparing those to the combination.

What we prefer is what we call a modified factorial. Unfortunately, that would be a very difficult concept to implement with only two experimental drugs available. It is really much easier to conceptualize with three drugs. It is possible, but you end up losing what is probably an important control arm in doing so.

Next slide. So when we talk about a modified factorial trial, a traditional factorial with three factors would be nothing. The three factors would be the combination of two factors and the three factors together.

What we would propose is knocking out all of the mono therapy portions of that. So it would be all of the two-drug combinations versus the three-drug combinations. And the comparisons you would make

would be, for example, all arms containing A to arms not containing A, all arms containing B to arms not containing B. This also will give us some preliminary information on which combinations of these drugs are more likely to be successful.

Next slide. As I have undoubtedly hammered home many times, there are advantages and disadvantages. The clear advantage in our mind is that such a study may offer a better chance of virological control in every arm and reduce the risk of persons being harmed by clinical trials.

This is a very important consideration to us. We understand the need for good data. We don't want to see people harmed doing it. And we would be the last to say that that is an easy paradox to reconcile.

This sort of design may delay further resistance to both the study agents and the elements of background therapy if there isn't complete resistance to those already and may allow median rank to the relevant merits of the various combinations. It's also a design that would be very, very attractive to potential participants.

Some of the disadvantages are that there is no true control arm in the study. There is no

optimized background therapy alone arm, which scientifically -- I mean, I look at this with two hats.

Scientifically I think that that is problematic. However, in the case of patients where there truly is very, very little chance that optimized background therapy is going to make any difference at all and there is imminent risk of serious morbidity or mortality, the rules may have to change a little bit. And the studies that actually are truly well-controlled may have to be done in slightly earlier populations.

There is an exception to that. And here I need to stress that this is absolutely my own opinion and not that of the Coalition for Salvage Therapy. I do think that there is room in patients. We simply do not see virologic response to do no-drug comparisons or placebo comparisons to see whether in patients who when we're not affecting the virus we're analyzing these drugs on, we're merely harming.

I need to stress that is not the coalition's position. It is mine. But I do think when we're not seeing a virologic response in people, it is very legitimate to ask: But why are we giving these drugs in the first place?

Other difficulties with this design are it is going to be more difficult to conclusively ascribe adverse events to any one agent. And if even this combination does not achieve virologic control, patients may have to endure more toxicities without commensurate benefits, but, of course, that's a risk in any trial.

Next slide, please. Endpoints. Well, in a true salvage population, percent below level of quantification is just not a realistic endpoint. Powering the trial will be extraordinarily difficult because it's very unlikely that you're going to get a major proportion of patients who do go below level of quantification. And so change in RNA may be a much more powerful and meaningful endpoint for such trials.

Where clinical endpoints are considered, the classic composite endpoint of progression or death may not be as relevant in these patients. It may be important to include major toxicities.

We're going to talk about lipodystrophy but things like major cardiovascular disease, incompetent clinical endpoints where clinical endpoint studies are done. So something along the lines of progression, major cardiovascular disease, diabetes, or death would be a possible clinical endpoint.

In any study that is done, we feel secondary endpoints should be rates of genotypic and phenotypic resistance to both the study agents and the background therapies. The issue here is that we are very interested into whether the study agents may actually preserve some of the benefit of the background therapy should any benefit be left.

Since we are in general defining these folks on the basis of a lack of virologic movement, HIV RNA may not be the primary endpoint. Also, as I speak to Dr. Deeks right here, there are some folks with elevated RNAs who seem to be doing pretty well.

So it may be realistic to think about preservation of CD4 count as endpoint in trials intra-salvage patients as opposed to changing to HIV RNA because we may not get those changes in HIV RNA. Yet, the patients may still be seeing some benefit.

Next slide. Some what do we need from the agency? Well, as I said in the beginning, sponsors need clear, unambiguous guidelines about what sort of novel studies are to be used in support of the NDA and perhaps even some over-encouragement to seek salvage indications.

We need open discussion into what the incentives are for research into further niche

populations, pediatric, injection drug users, and so forth. We need a commitment from everyone in the room to encourage and do meaningful expanded access programs, especially in the salvage population, and not just weeks before licensure.

To open the expanded access program two weeks before the drug is on the shelves is basically a slap in the face to the community. And it does you more harm than good in our eyes. It's not the intent of expanded access, and it's not okay with us. If you're going to do expanded access, get it out there as early as you can.

Co-enrollment of expanded access programs. This is something that has just been piloted this year or at least theoretically became acceptable, although it has not been actualized yet.

We heartily applaud this. And we would like to particularly tip our hats to Abbott because we feel that they have been the people who have actually had drug out there and have said: We have drug in our hands, and we are willing to do it now, as opposed to other companies who have said: Yeah. Well, we're into this in principle, but we don't have drug for you right now. Abbott said: We have lopinavir. We will do it today. And so we applaud them for that.

Next and last slide. This is perhaps my own diatribe. Long-term follow-up in AIDS trials has been an absolute disgrace. Even before the accelerated approval regulations were loosened, very few sponsors fully fulfilled their post-marketing requirements.

This is not an abstract or a purely political issue. None of the major protease inhibitor toxicities were seen prior to registration in terms of things like lipodystrophy, cardiovascular disease, insulin resistance.

I mean, we are aware of the elevated triglycerides but certainly the other more serious, life-threatening toxicities did not show up in those pivotal trials.

Now, we are glad those pivotal trials occurred quickly. We're glad that there was such unambiguous indication of benefit. The drugs were on the shelf. We would also like to see longer-term follow-up to see what the effects are of prolonged exposure to these drugs.

I mean, you look at some cases like AZT myopathy. I don't think that was actually formally recognized until five years after AZT was licensed. That's not acceptable.

Of course, during the AZT/DTC/ddI years, those were when the emphasis on Phase IV trials was much stronger. And even then, we didn't see full compliance.

We feel that this is not entirely a problem of the agencies in that you guys don't have the administrative tools to force compliance with Phase IV commitments.

I mean, basically you can pull a drug off the shelves or you can leave it on the shelves. And so I would hate to think that we would have to go to legislation on this, but we do feel it's important that the agency have some means of coercing that compliance with Phase IV commitments.

We're not exactly sure what that would look like, whether it would take the form of fines or incentives or how that would work, but we would really like to see some formal mechanisms for the agency to enforce Phase IV commitments.

This is particularly important in salvage patients, where it is quite possible there may be no virological indication response and, yet, there may indeed be a clinical benefit or there may indeed be a clinical harm. And it will only be longer-term studies that will determine that. So, especially in

populations where you really don't get a good virological comparison, we feel that long-term BOP is very important.

I think that basically hits all of our major points. Any questions?

ACTING CHAIRMAN GULICK: Thanks very much.

Are there questions? Mr. Levin?

MR. LEVIN: Jules Levin. I think it is important to fully appreciate that the community is diverse and the opinions are diverse. Okay? So I just want to comment on one thing that Carlton talked about, and that is factorial designs.

I don't think -- and other community people agree with me -- don't think that they -- not only that they are not useful, but I think they are counterproductive, a waste of resources.

And I don't think that an optimal regimen -- first of all, there are no three drugs right now for salvage therapy available right today. But if there were, I certainly don't think it's an optimal regimen to take standard of care plus A versus standard of care plus B plus standard of care plus three. That is not optimal therapy.

I would not enroll in a study like that, and I wouldn't like anyone with HIV, my best friend or

my worst enemy, to enroll in a study like that.

ACTING CHAIRMAN GULICK: Ms. Dee? Thanks, Jules.

MS. DEE: Lynda Dee from AIDS Action-Baltimore, the Treatment Action Group.

First of all, I would like to reiterate what Carlton says, that the consensus except for, Jules, as I remember, on the Coalition for Salvage Therapy was that factorial designs were very good for this population.

I think the problem is that we know that people, the true end-stage, late-stage salvage patients are going to need more than one drug with an optimal background regimen.

The problem with the drug companies has been that many of the drug companies are willing to work with another drug company to use two investigational drugs in one trial, but they haven't known what these trials are going to or should look like for the agency, what the agency is going to accept in order to get their compounds registered. I mean, it's just as simple as that.

I would assume that since we have had Dr. Schechter's wonderful presentation today, that that means the agency has put their imprimatur on these

kinds of factorial designs and that maybe the agency will indicate with the sponsors in their discussions that these are acceptable ways to answer a couple of questions at once, to get more bang for your buck, and to offer three drugs -- excuse me -- more than one drug, two drugs, two or three, to this population.

I would also say that the Coalition for Salvage Therapy disagreed with Carlton with respect to the placebo cell. And we thought that maybe a structured treatment interruption might be more appropriate there.

And as far as the post-marketing Phase IV stuff, I mean, I think that the agency just has to ask the sponsors. I think that you have that authority and you have that power. And I just think that sometimes you don't realize what power you have to say, "Look, this is what we want."

I mean, look at the EMEA. They said, "We want to know about lipodystrophy. We want to know what it means, definitions of it," and they're doing it. They're doing it. The sponsors are doing it among themselves, paying for it themselves. I think you just have to be a little bit more firm or proactive.

In the United States, these issues are

very politically, but hopefully, especially now with this new administration coming in, you will require the sponsors to do what the accelerated approval mechanism requires, and that is post-marketing studies.

ACTING CHAIRMAN GULICK: Let me stop us there at that point. We're going to have plenty of more opportunities today to get into some of the issues in terms of discussion.

I would like to thank the four presenters for their talks this morning. Let's take a ten-minute break and reconvene at 10 of 10:00.

(Whereupon, the foregoing matter went off the record at 10:38 a.m. and went back on the record at 10:55 a.m.)

ACTING CHAIRMAN GULICK: Welcome back from the break. We're ready to reconvene. I wanted to give Dr. Jolson an opportunity to respond to some of the comments that were made right before we went to break.

DR. JOLSON: I thought it would be worthwhile before we went on to respond to a couple of the comments that were raised just before the break.

I think there are two important issues. We're going to be talking a lot more about these as

the day goes on. So it's probably worth just presenting the agency's perspective in a nutshell. And then as Dr. Laessig speaks, she is going to be talking more about the regulatory perspective.

The first issue that was raised was: In concept is a factorial design acceptable to the agency? I know that we have gone on record in a written letter in 1999 to industry that we were extremely supportive of this approach because we think that it provides interpretable trial data and also, importantly, provides access to more than one novel agent for a patient because we are extremely concerned whenever we see trials such as either intensification studies or single-drug, add-on therapies that they are not providing optimal therapy to patients.

We have consistently articulated that issue whenever we're approached with a trial design. So I think we would be very, very supportive of trials that can accomplish both providing interpretable data and satisfactory treatment alternatives. And we have gone on record with pharmaceutical companies in that respect. Dr. Laessig when hopefully the proxima is fixed is going to be discussing more about that.

The second is the issue of Phase IV commitments. This comes up all the time in terms of

what is our regulatory authority vis-a-vis Phase IV commitments? When I say "our," I mean FDA as a whole.

There were two types of Phase IV commitments, and they have different legal teeth. One is the accelerated approval commitments, which are 100 percent binding. And if a drug company does not follow through with those Phase IV commitments for accelerated approval, the drug can be withdrawn from the market. And that is a legally binding Phase IV commitment.

So drugs that you have seen that have gone through the accelerated approval process, -- for example, nelfinavir comes to mind as one that has recently gone from accelerated to traditional approval -- it is by living up to that mandatory Phase IV commitment.

The other Phase IV commitments, the more typical types of things to do additional studies, it needs to be recognized that we ask for those. However, they are not legally binding. That's something that is in the law, and that really needs to be understood.

We have routinely been asking as Phase IV commitments for data on treatment-experienced patients. And, by and large, sponsors have worked

with us in good faith. But it needs to be understood that there is a limit to what we as an agency can require.

A lot of our time and energy is spent with working with companies and providing other incentives to get them to live up to their Phase IV commitments in a timely way.

MR. HOGAN: Dr. Jolson, just a quick comment. I would hate to think that I came across overly critical of the agency because we do recognize the enormous progress you guys have made and how aggressively you're confronting this issue.

Our concern is that withdrawal of a drug from the shelves is a very drastic step. It would be very nice if there were some intermediate administrative remedies because nobody wants to see a drug go off the shelf. Certainly it's of no service to the patient population to do so.

DR. JOLSON: Right.

MR. HOGAN: And, I mean, there are cases. There was an example of one of the nucleosides where they went four or six years before they fulfilled their clinical endpoint trials. So there has been some abuse of the system.

We would like to see you guys have some

tools to deal with that because nobody wants to see drugs pulled off a shelf.

DR. JOLSON: In general, we agree with you. And, as you know, to date no drugs from accelerated approval have been withdrawn. There are actually very few that still remain under accelerated approval.

The way that we encourage that to be done is through incentives. Labeling is a very, very powerful incentive. So to have, for example, 16 or 24-week clinical trial data in the label is not a very meaty label when it comes to trying to advertise the drug.

There is a strong incentive to put longer-term, more clinically relevant data showing prolonged viral suppression or whatever the endpoint is. That's really almost the best incentive to get companies to develop longer-term data.

MR. LEVIN: Just one brief thing. Certainly I don't want drugs taken off the market either. You sort of made a line between what is enforceable with Phase IV and what is not.

DR. JOLSON: Right.

MR. LEVIN: And I think that line is where you're talking about, things like, for example, we