

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE  
OPEN SESSION

Tuesday, July 15, 1997

8:00 a.m.

Armory Place  
925 Wayne Avenue  
Silver Spring, Maryland

MILLER REPORTING COMPANY, INC.  
507 C Street, N.E.  
Washington, D.C. 20002  
(202) 546-6666

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## 1 P R O C E E D I N G S

2 **Call to Order**

3 DR. HAMMER: Good morning. I would like to  
4 convene today's session on plasma HIV RNA as an endpoint in  
5 HIV clinical trials. I would like to begin by having the  
6 members seated at the table to introduce themselves for the  
7 record. I will start with David.

8 DR. FEIGAL: Good morning. I am David Feigal,  
9 FDA.

10 DR. FREEMAN: Donna Freeman, FDA

11 DR. ELASHOFF: Michael Elashoff, FDA.

12 DR. MURRAY: Jeff Murray, FDA.

13 DR. IACONO-CONNORS: Lauren Iacono-Connors, FDA.

14 DR. VALENTINE: Fred Valentine, NYU, Bellevue  
15 Hospital.

16 DR. DIAZ: Pamela Diaz, Chicago Department of  
17 Public Health.

18 DR. MATHEWS: Chris Mathews, University of  
19 California, San Diego.

20 DR. FEINBERG: Judith Feinberg, University of  
21 Cincinnati.

22 DR. HAMMER: Scott Hammer from the Beth Israel  
23 Deaconess Medical Center and Harvard Medical School in  
24 Boston.

1 MS. STOVER: Rhonda Stover, FDA.

2 DR. LIPSKY: Jim Lipsky, Mayo Clinic.

3 DR. EL-SADR: Wafaa El-Sadr, Harlem Hospital and  
4 Columbia University.

5 DR. CHINCHILLI: Vernon Chinchilli, Penn State,  
6 Hershey Medical Center.

7 DR. VERTER: Joel Verter, George Washington  
8 University.

9 DR. MODLIN: John Modlin, Dartmouth Medical  
10 School.

11 DR. FLYER: Paul Flyer, FDA.

12 DR. HAMMER: Thank you.

13 I would like to turn now to Rhonda Stover for the  
14 conflict of interest statement.

15 **Conflict of Interest Statement**

16 MS. STOVER: The following announcement addresses  
17 the issue of conflict of interest with regard to this  
18 meeting and is made a part of the record to preclude even  
19 the appearance of such at this meeting.

20 In accordance with 18 U.S. Code 208, general  
21 matters waivers have been granted to all committee  
22 participants who have interest in companies or organizations  
23 which could be affected by the committee's discussions of  
24 plasma, HIV RNA measurement as an endpoint in clinical

1 trials for drugs to treat HIV infection.

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

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

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

15 Thank you.

16 DR. HAMMER: Thank you. I would like to now  
17 introduce Paul Flyer from the Division of Antiviral Drug  
18 Products.

19 **Introduction**

20 DR. FLYER: Good morning.

21 [Slide.]

22 Yesterday, we focused on a series of large  
23 clinical trials which have been used to describe the  
24 relationship between treatment induced changes in HIV RNA

1 and CD4, and eventual clinical outcome as measured by  
2 disease progression.

3           We have seen that there is a strong relationship  
4 between the treatment induced changes in HIV RNA and  
5 clinical outcome. It is clear that the greater the initial  
6 drop of HIV RNA, the lower the risk of disease progression.  
7 We have also seen that the duration of suppression and  
8 changes in CD4 are also related to the risk of progression.

9           These presentations, as well as the published  
10 literature, suggest that it is appropriate to consider as  
11 one goal of treatment to be the long-term suppression of  
12 virus. Assuming for the moment that HIV-RNA is an  
13 acceptable long-term study endpoint, we can then ask what is  
14 the best way to structure long-term trials for evaluating  
15 HIV RNA.

16           The consideration of such an endpoint in clinical  
17 trials will not preclude us from the simultaneous  
18 consideration of treatment induced changes in CD4 when data  
19 from these trials become available. It is expected that  
20 trials of adequate size to detect differences in HIV RNA  
21 will also be large enough to detect differences in CD4.

22           Our concentration today for measuring changes in  
23 CD4 at today's meeting is driven both by its appeal as a  
24 direct measure of antiviral activity and the current

1 emphasis in clinical care on achieving maximal suppression.  
2           Given these issues, we think the design of trials  
3 to assess viral changes will pose special challenges.  
4 Today's talks were prepared to focus attention upon these  
5 issues of design.  
6           [Slide.]  
7           Previous trials have used both HIV RNA and CD4 as  
8 surrogates under the accelerated approval regulations. The  
9 definition of a surrogate under accelerated approval is an  
10 endpoint that is reasonably likely, based on epidemiologic,  
11 therapeutic, pathophysiologic, or other evidence to predict  
12 clinical benefit.  
13           Clinical confirmation was then required. We are  
14 planning to continue to base accelerated approval upon a  
15 dual consideration of HIV RNA and CD4, such as those  
16 measured in a way that was similar to those discussed  
17 yesterday.  
18           Our current discussions focus upon expanding the  
19 role of HIV RNA past its use as a surrogate under the  
20 accelerated approval regulations. As discussed previously  
21 by Drs. Feigal and Murray, FDA is proposing adding a new  
22 type of treatment indication, which is the suppression of  
23 HIV RNA. This indication would serve as the confirmatory  
24 trial for a drug approved under accelerated approval.

1           This being the case, we need to assess how to best  
2 study treatment-induced changes in HIV RNA, as well as  
3 changes in CD4 and disease progression to be able to  
4 adequately describe the long term treatment effects.

5           It should be noted that this discussion does not  
6 require that HIV RNA be accepted as a validated surrogate  
7 marker beyond that considered under accelerated approval.  
8 The labels will describe the initial and long-term effects  
9 of the drug with respect HIV RNA, and will not allow claims  
10 of clinical benefit to be made unless adequate clinical data  
11 is provided.

12           [Slide.]

13           In previous reviews, FDA and this committee have  
14 relied upon short-term changes in CD4 and HIV RNA as the  
15 basis of accelerated approval. In these discussions, in  
16 these submissions, we have looked at both means over time,  
17 as well as the mean over the overall period of 16 weeks or  
18 24 weeks. This has been called the DAVG. Other researchers  
19 have called it AUCMB.

20           This approach has a number of problems which we  
21 believe will become more pronounced in longer term studies,  
22 the first problem associated with the goal of therapy, which  
23 is quickly becoming the maximal suppression possible. This  
24 suggests that studying population averages may not be the

1 best way to summarize treatment effect in a situation where  
2 treatment is evaluated clinically for each study participant  
3 in terms of success or failure at a given time point.

4 Another problem is the inability to quantify virus  
5 for the majority of study participants in a number of recent  
6 trials. The use of an average presupposes that we can  
7 actually quantify the amount of virus. We have been seeing  
8 numbers 60, 70 percent undetectable, which makes figuring  
9 out, well, what is the mean change very problematic.

10 Finally, study participants will naturally switch  
11 when HIV RNA begins to rebound. The average for a fixed  
12 period of time will tend to mask real treatment differences  
13 as study participants begin receiving alternative therapies.

14 [Slide.]

15 Previous discussions suggest that we need to  
16 rethink our approach to evaluating treatments with respect  
17 to HIV RNA. As just mentioned, an important goal of HIV  
18 therapy is to achieve the maximal suppression possible and  
19 maintain the suppression for as long as possible. This  
20 means that we would like to characterize both magnitude and  
21 duration of viral suppression.

22 In thinking about these dual goals, it is crucial  
23 to keep in mind that study participants will almost  
24 certainly be aware of their own HIV RNA and CD4. The type

1 of design endpoints which will be best in this situation  
2 should not have produced missing data when study  
3 participants switch, nor tend to make the treatments look  
4 more similar after switching.

5           This suggests that we are less interested in  
6 quantifying virus than in comparing study participants based  
7 on both the adequacy of initial suppression, as well as the  
8 length of time of the suppression. These considerations  
9 have led us to be interested in clinical trials which rely  
10 upon time to lack of virologic response as the best way to  
11 summarize treatment effect with respect to HIV RNA.

12           [Slide.]

13           We have worked with industry, academia, and  
14 governmental agencies to examine large, recently completed  
15 clinical trials, which have monitored HIV RNA as part of  
16 their data collection efforts. Working with these groups,  
17 we have generated a number of analyses which we think will  
18 help us design these future trials.

19           The first issue that we have to deal with is what  
20 constitutes an initial response. The data presented  
21 yesterday address this issue. We have seen that the more  
22 pronounced the initial suppression, the lower the risk of  
23 disease progression.

24           The remainder of today's presentations will

1 address a number of additional design issues. One issue  
2 which will be addressed today is the length of clinical  
3 trials. It appears that trials should be at least 48 weeks  
4 in length, but that the optimal length may depend on the  
5 population being studied.

6 [Slide.]

7 Another area of interest is the best way to  
8 summarize the treatment effect. Our current thinking is to  
9 describe the time to lack of virologic response as measured  
10 by detectable virus in plasma. Data will be presented  
11 considering a number of different definitions of loss to  
12 response, as well.

13 Since study participants will certainly switch  
14 from assigned therapy if an inadequate initial response is  
15 achieved, we need to know how long individual study  
16 participants should be monitored and encouraged to remain on  
17 initial therapy before it is concluded that an adequate  
18 response will not be achieved.

19 Evidence suggests that there is a risk of  
20 prematurely concluding that a particular regimen is  
21 inadequate.

22 [Slide.]

23 So once we arrive at a basic design and an  
24 approach, we need to then consider how to modify this

1 approach based upon the particular population being studied,  
2 we are really talking basically now about a generic  
3 protocol, but, of course, special populations we would like  
4 to modify it to reflect the characteristics of those  
5 populations.

6           So it seems likely that the design will have to be  
7 modified based upon the characteristics of the population  
8 being studied, so that we are going to see data on the  
9 relationship between baseline HIV RNA and CD4, as well as by  
10 previous treatment and disease state in the analyses that  
11 are coming up.

12           [Slide.]

13           We now move on to the data presentations. The  
14 first presentation will be by Dr. Chodakewitz of Merck, who  
15 will present data related to the time to virologic response.  
16 This will be followed by three presentations addressing both  
17 time to virologic response, as well as longer term data  
18 describing the durability of response.

19           Dr. Quart from Agouron, Dr. Hall from Boehringer  
20 Ingelheim, and Drs. DeMasi and Smiley from Glaxo-Wellcome  
21 will make these presentations. These presentations will  
22 then be followed with an FDA summary by Dr. Elashoff, who  
23 will also discuss additional study results prepared by other  
24 organizations who will not present today.

1                                   **Viral RNA Changes in Response to**  
2                                   **Antiretroviral Treatment**

3                   DR. CHODAKEWITZ: Good morning.

4                   [Slide.]

5                   I am Jeff Chodakewitz from the ID Clinical  
6 Research group at Merck, and appreciate the opportunity to  
7 participate in this morning's discussion of viral RNA  
8 changes in response to antiretroviral therapy.

9                   Based on the goals of the meeting today, and also  
10 based on discussions that we have had with members of the  
11 FDA Antiviral Division, my discussion is going to focus on  
12 the characterization of viral RNA changes, particularly the  
13 early viral RNA changes among patients who achieved a viral  
14 RNA level below 500 copies per mL in several indinavir  
15 trials.

16                   When approaching this question, we identified a  
17 couple of primary objectives.

18                   [Slide.]

19                   First, we wanted to define the time course of  
20 viral RNA response among those patients who do have  
21 successful suppression of viral RNA levels to below 500.

22                   Secondly, we wanted to evaluate any potential  
23 relationships between how long it takes to achieve that  
24 level below 500 copies and various baseline factors.

1           In looking at these objectives, we then went on to  
2 identify a patient population for whom we had data to  
3 conduct these analyses.

4           [Slide.]

5           This slide just summarizes the patient population.  
6 It was individuals who had at least 24 weeks of viral RNA  
7 data and participated in one of three indinavir Phase  
8 II/Phase III trials, either Protocols 028, 033, or 035, and  
9 this is a data set that was part of our NDA last year.

10           All of these trials were double-blind, randomized,  
11 multicentric trials and patients were randomly assigned to  
12 one of three treatment groups. They received either  
13 nucleoside analogs alone, indinavir monotherapy, or a  
14 combination of indinavir and nucleoside analogs, and the  
15 analyses that I am going to show you focus specifically on  
16 the treatment groups where patients received indinavir alone  
17 or in combination, and most of that combination therapy was  
18 indinavir with zidovudine.

19           The protocols also shared a couple of other common  
20 entry criteria. For instance, in all the trials, the  
21 baseline CD4 count needed to be between 50 and 500, and  
22 patients who had prior protease inhibitor use were excluded.  
23 Only one of the trials, the smallest one, had an entry  
24 criteria for viral RNA greater than 20,000 copies, the other

1 two protocols did not.

2 [Slide.]

3 I would just like to make a couple of comments on  
4 how we conducted the analysis. First of all, we had viral  
5 RNA measurements at baseline and at every four weeks during  
6 the course of the study. A number of the patients also had  
7 viral RNA at week 2 of the study.

8 We had to define a response or the responder  
9 population that we wanted to use in our analyses, and we  
10 chose a definition for patients having two consecutive viral  
11 RNA measurements less than 500 copies per mL.

12 Now, this is a stringent definition and we did  
13 that intentionally because I think we believe, and you will  
14 hear more data I believe to suggest this, that this is the  
15 best way for this type of drug to get a very durable  
16 antiviral effect.

17 Using that definition, 56 percent of the patients,  
18 or 204 of 366 individuals for whom we had data receiving  
19 indinavir met that definition, and it is really this 204  
20 patients who will be the subject of the analyses I will be  
21 showing you.

22 Lastly, looking at time to response, the way we  
23 defined that was the first time point in which a viral RNA  
24 less than 500 copies/mL was observed.

1 [Slide.]

2 Just to give you a sense of the patient  
3 population, just summarized here are some demographics both  
4 for the total population of 366 patients and the responder  
5 group that will really be the focus of the analysis. You  
6 can see that the patients were about 85 percent male, about  
7 85 percent caucasian. They had a median baseline CD4 count  
8 of around 200 and a median baseline viral RNA of around 20-  
9 or 30,000 copies/mL, and about half of the patients, based  
10 on the randomization scheme, received combination therapy.

11 [Slide.]

12 This graph summarizes the temporal relationship  
13 that we saw in terms of the time to viral RNA level below  
14 500, and again, this is only for the patients who met the  
15 definition of response.

16 Let me just briefly show you how the data is  
17 presented all my slides will be in this format. On the x  
18 axis is study week starting with time zero at the initiation  
19 of therapy out to 24 weeks. On the y axis are the  
20 proportion of patients who have not yet met the definition  
21 of response and therefore have viral RNA levels greater than  
22 500.

23 By definition, because we excluded those few  
24 patients who at baseline had a viral RNA less than 500, all

1 patients had a viral RNA greater than 500 at time zero, and  
2 because we have only selected those patients who met our  
3 definition of response. Again, by definition, all the  
4 patients will have reached that level of response, so you  
5 will be at zero by the end of 24 weeks.

6           Lastly, in the legend, you can see the individual  
7 treatment groups both in terms of the treatment regimen and  
8 the protocol that they were in, and following that in  
9 parentheses are the number of patients who met the  
10 definition of response and the total number of patients for  
11 whom we had data available in that treatment group, so the  
12 patients receiving monotherapy had about 40 to 50 percent  
13 response, those receiving combo with indinavir and  
14 zidovudine about 50 to 60 percent, and those receiving  
15 triple therapy about 90 percent.

16           Now, turning your attention to the different  
17 profiles among the six treatment groups, while I think there  
18 is some evidence of variability, particularly at the early  
19 time point, what I think you can also see is there really is  
20 a very similar pattern of response among all the treatment  
21 groups. I think notably, this remains the case even though  
22 we are comparing treatment groups that differ in the  
23 proportion of patients who meet the definition of response,  
24 the pattern of response among those responding really is

1 quite similar.

2           Now, given that observation, we felt it was  
3 reasonable to combine these patients to do further  
4 exploration, and that is shown on this next graph.

5           [Slide.]

6           So the same patients who you just saw are now  
7 combined into a single profile 24 weeks and proportion  
8 greater than 500. What I think you can see is that by week  
9 4, about 60 percent of those patients who are going to  
10 respond, and by week 8, about 80 percent of those patients  
11 who are going to respond, had done so.

12           But the flip side of that is that there is still a  
13 significant number of patients who take longer to respond,  
14 and, in fact, one needs to go out to week 20 before all the  
15 patients who are going to respond have done so.

16           In looking at the profiles and the patients who  
17 respond later, other than having an RNA that falls more  
18 slowly, there is really no overt difference otherwise  
19 between these patients and patients who respond earlier.

20           I would also like to make one other point that is  
21 not immediately obvious from this slide. I think it would  
22 just be natural for patients or physicians, when they are  
23 caring for patients who do not have a viral RNA less than  
24 500 very early on, to at least look at the magnitude of the

1 fall at these early time points for some sense of how  
2 patients are doing.

3 I think, therefore, it is important to note that  
4 looking at patients who respond later, that there are about  
5 15 or 20 percent of patients at week 2 and 4 who do not even  
6 have a 1 log decline in viral RNA, and these are inpatients  
7 who we know by definition are going on to respond.

8 So I think that that has some implications as  
9 patients make some treatment decisions, and I think, as was  
10 mentioned by Dr. Flyer, there is also an implication in  
11 terms of treatment design in clinical studies in terms of  
12 how points at which switching antiretroviral therapy is  
13 considered.

14 Having defined this, we went on to see whether  
15 there were barriers to baseline factors that might influence  
16 the rate at which viral RNA falls.

17 [Slide.]

18 This first analysis shows the same 204 patients,  
19 but this time divided based on their baseline viral RNA.  
20 These are patients who, at baseline, had less than 10,000  
21 copies, 10 to 20, 20 to 50, and greater than 50,000 copies  
22 at the beginning of treatment, and I think what you can see  
23 is those patients who have higher viral RNA at baseline tend  
24 to take longer to have their viral RNA levels reach less

1 than 500 copies/mL, and again this is just the responding  
2 population.

3 We went on to evaluate other potential variables  
4 that might influence time to response, but in our analyses,  
5 based on CD4 count, gender, and race do not have any impact  
6 among responders on the time to viral RNA less than 500.

7 Lastly, we took advantage of some additional data  
8 we had to look at one further related question, and that had  
9 to do with the time it took to get to a viral RNA level that  
10 was lower than 500 using a more sensitive assay.

11 In one of our protocols, Protocol 035, for all the  
12 patients whose viral RNA had fallen to less than 500  
13 copies/mL, we also had reassayed those samples using the  
14 ultra-sensitive assay, which we feel comfortable using a  
15 cutoff of 50 copies/mL, and the result of that analysis is  
16 shown here.

17 [Slide.]

18 We had 42 patients who were receiving indinavir  
19 either alone or in combination, and of those 42 patients, 34  
20 of them also had viral RNA levels less than 50, and it is  
21 those 34 patients who are presented in this summary.

22 For the less than 500, you can see a pattern very  
23 similar to what I have already shown you overall with it  
24 taking about 16 weeks for all the patients to have a viral

1 RNA less than 500. Yet, you can see that it takes quite a  
2 bit longer, actually 28 weeks, before all the patients who  
3 are going to fall to below 50 copies/mL actually do so.

4 So that not only do we have to adjust expectations  
5 in terms of some things like the starting viral RNA level,  
6 but we also have to do so based on the viral RNA assay that  
7 is being selected.

8 [Slide.]

9 In conclusion, then, all the patients in the  
10 population that we examined, who were going to achieve a  
11 viral RNA below 500 copies/mL, had done so by week 20 of  
12 therapy, and that higher baseline viral RNA levels were  
13 associated with a longer period of time before RNA levels  
14 actually dropped to below 500.

15 [Slide.]

16 I think there are also some clinical implications  
17 of the results that I have shown you, both for individual  
18 patients and in terms of trial design.

19 I think it is important that there be realistic  
20 expectations for the time course of viral RNA response if we  
21 are to avoid unnecessary changes in therapy that are  
22 actually being quite effective.

23 Also, we further have to adjust our expectations  
24 for patients who have higher baseline viral loads or when

1 the assays that are being used have greater sensitivity than  
2 the standard one.

3           Lastly, very early declines in viral RNA are  
4 variable even among patients in whom we know less than 500  
5 copies/mL is going to be reached.

6           That concludes my presentation and I hope this  
7 information is useful in the context of the discussion  
8 today.

9           DR. HAMMER: Thank you, Jeff. That was very  
10 interesting.

11           We are going to have some time for general  
12 questions later, but are there any immediate clarification  
13 questions from the panel? Jim.

14           DR. LIPSKY: In the 44 percent of the patients who  
15 didn't meet the criteria, what did their viral pattern look  
16 like, were there any hints early on that something bad--we  
17 don't know if it is bad, we presume it is--but things  
18 weren't going in what we had hoped to be the right  
19 direction?

20           DR. CHODAKEWITZ: It was hard to distinguish. The  
21 patients--and we are still doing these analyses--the  
22 patients who were going to go to less than 500, did tend to  
23 have larger drops at the early time points, but there was a  
24 lot of overlap with patients, as I said, who were going to

1 go to less than 500, not having large drops, and conversely,  
2 patients, not everybody who had a large drop went to less  
3 than 500.

4 DR. LIPSKY: So obviously, that is an important  
5 issue to know, you know, for the person who you know is  
6 going to respond, you can say, yes, stay with it, but the  
7 person who isn't, you don't know how long to stay with it.

8 DR. CHODAKEWITZ: Right.

9 DR. LIPSKY: The other thing, did anybody  
10 mathematically model even with the ultra-sensitive assay  
11 down to 50, you know, what would be the expectation for how  
12 long one should wait? In other words, you know, to get down  
13 to 50 or below, it looks like it is possible that you could  
14 model that.

15 DR. CHODAKEWITZ: No, we haven't done that formula  
16 yet. I think that we are still going to need to accrue more  
17 patients with that assay level, but I think this gives us  
18 some hint that we would agree that it is going to need to be  
19 looked at separately, because it is reasonable to think that  
20 that is going to be different.

21 DR. HAMMER: Thank you, Jeff.

22 DR. FEINBERG: I want to ask a brief question. I  
23 know at the outset you said you were only going to show us  
24 the data for the people who met the definition of response,

1 but I wonder if you have any--I think this is where Jim was  
2 heading, too--what you could tell us about those people who  
3 did not meet this definition, you know, how were they  
4 different, did they have different baseline viral loads?

5 I am struck that in clinical practice, of course,  
6 you see patients who have viral loads in excess of a  
7 million, but somehow those patients never seem to show up in  
8 anybody's study.

9 DR. CHODAKEWITZ: Well, I guess I would say a  
10 couple of things. I think once you start talking about who  
11 is going to respond rather than characterizing the  
12 responders, there obviously are more variables, and one of  
13 the things that come into play there is also the treatment  
14 that they are going to receive.

15 For instance, a high proportion of the patients,  
16 50 percent of the ones in this study, were on indinavir  
17 monotherapy. Now, protease monotherapy is not the way most  
18 patients are being treated, so that obviously influences  
19 that, and the only way we could really answer that is for  
20 this set, which may not be completely representative of the  
21 way that drugs are being used now.

22 I can tell you just briefly looking at some of the  
23 different factors, and these often are confounded with each  
24 other and we haven't done that analysis yet, but that higher

1 viral RNA at baseline, a smaller initial drop in viral RNA  
2 and a lower CD4 count did tend to be associated with a lower  
3 likelihood of getting to RNA less than 500, but again, as  
4 you might expect, there is a lot of potential  
5 interrelationships between those different factors.

6 DR. HAMMER: Thank you.

7 DR. EL-SADR: If you took a population that had  
8 one value of less than 500, did you have any where they  
9 actually go down to less than 500 and bounce a little bit  
10 back up? I am just thinking in real life, you know, you  
11 have a very stringent diagnosis, you know, definition of two  
12 consecutive less than 500.

13 DR. CHODAKEWITZ: We did look at that. There are  
14 some patients who do bounce, come down, bounce up and down  
15 again, but I think one thing that we have to keep in mind is  
16 that we just did this as a straight intention to treat, so  
17 we do have to also correlate that to what the patients were  
18 doing clinically, so we didn't differentiate whether  
19 patients transiently stop their therapy versus that was the  
20 natural course of their viral RNA on treatment.

21 I think that there is variability. Just in the  
22 broader sense, I can tell you that we have seen variability,  
23 but most of the time when patients are going to go down to  
24 less than 500, usually, once they get there, it tends to be

1 pretty stable. That is not as true for the less than 50,  
2 where I think we have seen more bouncing underneath even in  
3 patients who continue to have a very durable antiviral  
4 effect.

5 DR. HAMMER: Thank you.

6 I think we should move on. The next speaker is  
7 Barry Quart from Agouron.

8 DR. QUART: Thank you. We appreciate the  
9 opportunity to participate in this quite important  
10 discussion.

11 [Slide.]

12 For this discussion, the FDA has requested that we  
13 present information from our Study 511 in order to set the  
14 stage for this afternoon's discussions of setting up  
15 appropriate studies and utilization of surrogate markers as  
16 an endpoint for traditional approval.

17 In Study 511, it was a three-arm trial of which I  
18 am only going to be talking about the patients who were on  
19 all three drugs including the two doses of nelfinovir 750 mg  
20 three times a day, and 500 mg three times a day. I won't be  
21 discussing anything about the control arm in this particular  
22 discussion.

23 One of the unique features of this trial, which I  
24 think was somewhat startling to the agency when we proposed

1 it, but now it is becoming more common and I think very  
2 important for the treatment of patients, is that we  
3 initially set up to have surrogate markers, either viral  
4 load or CD4 count, as an endpoint, and when patients reached  
5 a return to baseline in either viral RNA or CD4 count, that  
6 patient, particularly if they were on the placebo arm, could  
7 be switched, and was switched, to active therapy.

8 In other words, it was a way of getting patients,  
9 who were not doing well in terms of surrogate markers, to  
10 move them into more active therapy. I will be discussing a  
11 little later about the pros and cons of doing that and how  
12 we think that it should be done in the future.

13 For this trial, we utilized the patients who are  
14 antiretroviral naive and no prior protease inhibitors. The  
15 patients' baseline characteristics are here. They had a  
16 mean of 288 CD4 cells and HIV RNA of 153,000 copies.

17 [Slide.]

18 The definitions--to set the stage for the  
19 discussion--are very similar to what you just heard from  
20 Jeff, and that is that treatment response for this analysis  
21 was defined as two consecutive values below the limit of  
22 quantification, and the limit of quantification that I will  
23 be talking about across most of these slides is 1,200  
24 copies/mL, which is the agreement that we have with the

1 Agency, although we are still discussing that lower limit of  
2 quantification.

3 We used the bDNA assay from Chiron for all of  
4 these studies.

5 The time to response is the time to get to the  
6 first of these two values below limit of quantification.

7 Virologic failure, again, for this analysis, is  
8 two consecutive HIV measurements that rebounded after the  
9 patient was considered a responder.

10 Then, obviously, the duration of response is then  
11 the interval that it took for that patient to go from a  
12 responder to virologic failure.

13 [Slide.]

14 We are going to use this information now to answer  
15 what I think are some very basic questions. These are  
16 questions that were posed to the committee and which we  
17 believe are quite important for designing therapy in the  
18 future.

19 The first question, which is similar to what you  
20 just heard, is how long it takes to reach a treatment  
21 response, again, the definition of two consecutive values  
22 below limit of quantification, and is there an impact of  
23 baseline characteristics.

24 [Slide.]

1           This is our Kaplan-Meier curve of time to  
2 response. Again, as you just saw, you have a very rapid  
3 decline in viral load, and so you see these are the percent  
4 of patients who are becoming responders or, on this  
5 particular case, this is 100 percent who are nonresponders  
6 to start, and then by two weeks you see, in fact, more than  
7 50 percent of patients are considered responders having  
8 reached that first value below the limit of quantification.

9           Then, in fact, you have the vast majority of  
10 patients are responders by eight weeks, but in fact, as  
11 previously noted, it does take longer for a few patients.

12           [Slide.]

13           If we take a look at baseline characteristics, and  
14 also in this particular case, different cut points in terms  
15 of different assay values, obviously, the lower you go, it  
16 takes longer to get there. So if we use the data in terms  
17 of the lowest limit of quantification reasonable with this  
18 assay, and then looking at different cut points, the lower  
19 that you look in terms of limit of quantification, the  
20 longer it takes, but the difference is actually not very  
21 significant in this particular case.

22           [Slide.]

23           Also, the higher you start, the longer it takes to  
24 get down to limit of quantification. Again, the patients

1 that had greater than 100,000 copies/mL, it took slightly  
2 longer although the difference here is just a few weeks.

3 [Slide.]

4 In terms of baseline CD4 count, we really didn't  
5 see any difference in terms of time to response. Then, as I  
6 noted, there were a few patients in this particular case,  
7 six patients, who took longer than most. In fact, one  
8 patient took substantially longer.

9 In looking at the baseline characteristics of  
10 these patients, we really have not noted anything  
11 specifically different about them. We are still trying to  
12 evaluate these patients and look at compliance issues and  
13 see whether that was a factor.

14 [Slide.]

15 The next question we would like to evaluate is  
16 what type of short-term virologic response is associated  
17 with a durable HIV reduction, in other words, from our point  
18 of view, how long do you have to look at viral to understand  
19 that it is going to be durable and also how long do you have  
20 to look at viral load to be able to differentiate between  
21 active arms of the study.

22 [Slide.]

23 In this case, we will be looking at actually the  
24 two different doses that were evaluated in this study, and

1 this is the 750 mg and the 500 mg dose of Viracept in  
2 combination with AZT/3TC, and as you see that, in fact, very  
3 early on one looks at--this is the duration of response so,  
4 so we are looking at all responders and then how long those  
5 patients respond, that early on there is very little  
6 difference between the arms, that it is when you really get  
7 out to 16 to 24 weeks that you start to see a difference in  
8 terms of the durability of response, and it is our belief  
9 that you really need to get out to about 24 weeks or six  
10 months to one year in terms of being able to clearly define  
11 the durability of response.

12           There is actually very few patients, as you can  
13 see, that lose viral response beyond six months, so that the  
14 first six months is a very good indicator in terms of what  
15 is going to happen for the next six months.

16           [Slide.]

17           As has been discussed in the past, that  
18 previously, the Agency and companies have utilized AUCMB, as  
19 well as mean change in HIV RNA as measures of virologic  
20 response, and have used those to determine both efficacy, as  
21 well as whether or not a product was registerable.

22           It was interesting to note that in our particular  
23 study, we found that there was very little difference  
24 between the two doses for these measures, that it was not

1 until you looked at the percent responders that you started  
2 to see a statistically significant difference in terms of  
3 the two different dose arms, so that we feel that, in fact,  
4 it is percent responders that is a much more sensitive  
5 metric in terms of evaluating active arms.

6 [Slide.]

7 Do baseline factors impact on the virologic  
8 response? Do they impact on the durability of response?

9 [Slide.]

10 Here, we are looking at a combination of both  
11 arms. This is both the 500 and 750 arm, and all responders,  
12 and looking at baseline CD4 count, and we see that, in fact,  
13 patients who have CD4 count, here in green and in blue, of  
14 basically greater than 100 to 300, and less than 100 cells,  
15 were significantly different in terms of their durability  
16 compared to patients that had greater than 300 cells.  
17 Again, this is across the two doses.

18 So one might conclude, in fact, CD4 count as a  
19 baseline characteristic, was important in terms of  
20 durability of response.

21 [Slide.]

22 But we then took a look at just the 750 mg group,  
23 which is our approved dose and what we believe to be the  
24 optimal therapy, and you see, in fact, that there now is no

1 significant difference in terms of CD4 count regarding  
2 durability. So we don't believe the CD4 count is an  
3 important marker in terms of duration of response.

4 [Slide.]

5 On the other hand, baseline HIV RNA was an  
6 important marker. You see here that patients with greater  
7 than 100,000 copies had less durable response although, in  
8 fact, even out to one year, you see that 70 percent of  
9 patients are still responding, but it was less durable than  
10 patients with lower HIV RNA at baseline.

11 [Slide.]

12 And that is also observed when we take a look at  
13 just the 750 mg group. It is interesting to note that  
14 patients who had less than 50,000 HIV RNA at baseline have  
15 extremely durable response with 95 percent still responding  
16 at one year, so there really is a difference in terms of  
17 baseline values.

18 [Slide.]

19 If we take a look at time to response as a marker,  
20 in fact, we saw no difference. It didn't matter whether the  
21 patient was a rapid responder or, in fact, took longer than  
22 the median of 15 days.

23 [Slide.]

24 Is it possible to have a durable partial response

1 was one of the questions that was posed by the Agency.

2 [Slide.]

3 In fact, we did find some patients who so-called  
4 have a new setpoint in terms of their RNA. These are  
5 patients that had a baseline of greater than 5 logs to start  
6 with, they were responders, and then they had a relapse. In  
7 other words, they had value above the limit of  
8 quantification, but their viral load did not go back up to  
9 baseline, it remained stable in this particular analysis out  
10 to 36 months of followup after relapse at about 4 logs.

11 I can't comment in terms of whether or not those  
12 were particularly different in terms of their baseline  
13 characteristics. We really haven't had a chance to look at  
14 those patients.

15 [Slide.]

16 One of the questions that I think is quite  
17 important is how many data points are needed to discriminate  
18 between the loss of virologic response and assay  
19 variability. We heard a lot about assay variability  
20 yesterday. In fact, we saw quite a few patients who had  
21 this kind of response where they went down very quickly to  
22 the lower limit of quantification, and then during therapy  
23 we saw a single point above the limit of quantification or,  
24 in fact, sometimes more than a single point.

1 [Slide.]

2 In looking at the database we found that, in fact,  
3 there were 28 patients out of the 177 responders on the two  
4 doses that had a single value and then went back down to the  
5 limit of quantification and remained a long-term responder.

6 So, clearly, a single point above the limit of  
7 quantification shouldn't be considered a treatment failure.  
8 You would classify way too many patients as a failure.

9 We used two measurements above the level of  
10 quantification. In this case, that actually meant that five  
11 patients who were long-term responders were inappropriately  
12 classified as a treatment failure. They were up for two  
13 values and then came back down without any treatment change  
14 and went on to have a durable response.

15 So, even with using two, which is our definition,  
16 we do misclassify some patients. If we used three, we would  
17 only misclassify one patient, but I think that the general  
18 consensus is that waiting for that third one might be too  
19 long of a wait for some patients.

20 [Slide.]

21 As I noted in the introduction, we utilized CD4  
22 count return to baseline as another definition of treatment  
23 failure, and there was some discussion yesterday of the  
24 importance of the CD4 count and how it should be used.

1           So I thought it is important to bring it up in  
2 terms of should CD4 count be used to determine treatment  
3 failure. The conventional wisdom, in fact, is that CD count  
4 tends to go up and stay up longer than viral load, and then  
5 should patients who experience virologic failure have only  
6 one drug added or switched.

7           This is not a question that was posed by the  
8 Agency, but an issue that we believe is quite important in  
9 terms of trial design, and since we had a treatment switch  
10 in our studies, we thought it was worthwhile bringing this  
11 up.

12           [Slide.]

13           So as I noted in Study 511, we utilized either RNA  
14 or CD4 count, and to our surprise, in fact, of the patients  
15 who met this defined criteria, virtually all of them were  
16 based on CD4 count, and there were very, very few who  
17 actually reached this treatment criteria based on RNA.

18           What we found, in fact, in some patients,  
19 particularly in the first few months, that there was lack of  
20 concordance between viral load and CD4 count. There were 14  
21 patients whose CD4 count returned to baseline in the 750-mg  
22 arm, and yet, 90 percent of those patients actually had  
23 viral load that remained below limit of quantification.

24           [Slide.]

1           This is not to say that we didn't have a robust  
2 CD4 count response. In fact, this is the CD4 count response  
3 for the two doses that was over 150 cells at six months, and  
4 continues to rise, but in the early period, during the first  
5 two months, you do see a certain amount of variability, and  
6 we don't believe that CD4 count is appropriate for use in  
7 terms of defining whether a patient is a responder or a  
8 treatment failure, particularly in the first few months.

9           [Slide.]

10           The second question is, is it appropriate to just  
11 simply switch or add a new drug when patients do reach this  
12 treatment failure criteria, and as I noted in our study,  
13 patients, particularly on control, placebo was changed to  
14 active therapy.

15           Here we have patients who actually were treatment  
16 failures at 24 weeks on AZT/3TC. Over a course of several  
17 months, Viracept was added to their therapy. Some sites,  
18 unfortunately, were later than others in getting Viracept  
19 included in the protocol, but these are now patients who  
20 were previously failures on AZT/3TC, were switched to just  
21 adding a single new drug Viracept, and this is their  
22 response.

23           As we see, we get about a 50 percent or so  
24 response in those patients, in other words, 50 percent are

1 now below limit of detection, but the question is are we  
2 doing the best thing for those patients by simply just  
3 adding a drug to a regimen that has failed in terms of  
4 virologic response.

5 [Slide.]

6 Clearly, if one looks at this profile, and  
7 particularly the outcome of adding now the third drug, we  
8 don't think that that equals starting with three new drugs  
9 at the same time, which is the response you get when you  
10 start in the Study 511, starting all three drugs at once  
11 where you get a 90 percent response out to one year, so  
12 that, in fact, all of our new studies we now require that  
13 more than one drug either be added or changed, trying to get  
14 maximal activity, and not just sequential therapy for the  
15 patient.

16 [Slide.]

17 So, in conclusion, for maximal suppression of HIV  
18 RNA, it reached in about four weeks for the majority of  
19 patients, although some patients do take longer than others.  
20 The time to reach maximal suppression was dependent only on  
21 the baseline HIV RNA, so how high you started and how low  
22 you were looking at in terms of what the lower limit of  
23 quantification was.

24 We think that clinical trials of 6 to 12 months

1 are more than adequate for evaluating the durability of  
2 response and also being able to evaluate different potent  
3 drug regimens.

4 We did find in terms of durability that patients  
5 with lower baseline HIV RNA less than 100,000 particularly  
6 showed a more durable response.

7 [Slide.]

8 Treatment failure should be defined carefully to  
9 avoid switching patients that are actually still responding  
10 to therapy, and so when this discussion occurs later in  
11 terms of what is treatment failure, we need to make sure  
12 that we classify these patients appropriately.

13 We think that using the definition of two  
14 consecutive HIV RNA measurements above the limit of  
15 quantification is appropriate, but we need to understand  
16 that that may actually call some true treatment responders  
17 treatment failures.

18 We also don't believe that it is appropriate to  
19 use CD4 count for that determination, as I mentioned, and  
20 that based on the data that we have from our studies where  
21 we did switch patients, we believe that adding a third drug  
22 after patients have met the treatment failure criteria is  
23 not equivalent to starting with multiple new drugs, and we  
24 do not believe that it is appropriate just to simply add a

1 single drug every time a patient fails.

2 Thank you very much.

3 DR. HAMMER: Thank you.

4 Are there any clarification questions? Mark.

5 MR. HARRINGTON: Well, it is not really a  
6 clarification. I just wanted to take issue with the  
7 conclusion No. 3 that clinical trials of 12 months in  
8 duration should be sufficient in terms of durability,  
9 because if we are comparing two active regimens, it may be  
10 sufficient for regulatory purposes to get the drug out under  
11 accelerated approval. I don't think it is sufficient for  
12 public health purposes or for optimizing therapy or finding  
13 out about longer term side effects. Since 80 percent are  
14 responders, we want to know how long those responses are  
15 going to continue in both active arms.

16 So I think it might be good for the accelerated  
17 portion of the approval, but not for--there still needs to  
18 be longer term followup in comparative studies.

19 DR. HAMMER: Thank you.

20 DR. QUART: We wouldn't disagree. These patients  
21 are still ongoing in long-term followup.

22 DR. HAMMER: Judith and then Wafaa.

23 DR. FEINBERG: I have two just clarification  
24 questions for the way things were defined.

1           When you defined people as failures who had two  
2 measurements above the limit of detection, is that an  
3 arithmetically above the limit of detection or in some  
4 logarithmic change above the limit of detection? I wasn't  
5 clear.

6           DR. QUART: In this particular case, that was  
7 simply an arithmetic number that if the limit of detection  
8 is 1,200, it would be a value of 1,201.

9           DR. FEINBERG: Okay, because again this pertains  
10 to the fact that in the rules of clinical practice, it is  
11 common to see patients' values, even patients that you  
12 believe to be compliant and well motivated, to see a  
13 fluctuation around the limit of detection, which in my  
14 hospital is 400 copies, and it is common to see people below  
15 the limit of detection for a few months, and then there are  
16 420 copies, 500 copies, and then it goes back down again.

17           I am unsure--I mean I don't change therapy in  
18 those patients--I am unsure that that really means that they  
19 are failing and I concerned about the definition of that in  
20 trials.

21           Also, at the beginning of your talk, you said that  
22 this would be based on the FDA's determination that the  
23 limit of quantification in your studies was going to be  
24 1,200 copies, and then there was at least one subsequent

1 slide where the limit was, the footnote said it was 500  
2 copies, and so is it appropriately footnoted in all the  
3 pages where the limit of detection used was something other  
4 than 1,200?

5 DR. QUART: Yes, that is correct.

6 DR. FEINBERG: Okay.

7 DR. HAMMER: Wafaa.

8 DR. EL-SADR: I know the data showed that there  
9 was no association of the duration of the response and  
10 baseline CD4, but did you see any association between  
11 duration of response and CD4 response by whatever  
12 definition, did you look at that?

13 DR. QUART: I can't say that I have an absolute  
14 answer for you. In general, what we found is, is that there  
15 was good concordance at least out in time between those  
16 patients who had a virologic response and a durable  
17 virologic response and an improvement in CD4 count.

18 Certainly, when one takes a look at the overall  
19 picture, we see that, but I honestly can't tell you on an  
20 individual basis.

21 DR. HAMMER: In the patients that relapsed and  
22 then seemed to stay stable at a lower RNA copy number than  
23 at baseline, some of those extended out 28 to 32 weeks.  
24 Have you looked at the protease sequences from those

1 isolates?

2 DR. QUART: We may have that, but I honestly don't  
3 have that information.

4 DR. HAMMER: That would be an important issue as  
5 far as another component of what to do with future treatment  
6 switches as we learn more about how to use resistance in  
7 clinical monitoring.

8 DR. QUART: Right.

9 DR. HAMMER: Jim.

10 DR. LIPSKY: That is I think the first time  
11 resistance has been mentioned this morning. Has reasons for  
12 failure been looked at as resistance patterns, did you look  
13 at resistance patterns?

14 DR. QUART: We are doing an analysis of those  
15 patients who so-called failed, and we have samples stored,  
16 and they are being evaluated, but I don't have any  
17 information with me in terms of individual patients who met  
18 the criteria in terms of whether or not they have a  
19 genotypic or phenotypic change.

20 In fact, these definitions, as described here, are  
21 really somewhat artificial. This was a post-hoc analysis of  
22 data looking at it in a different way than the study was  
23 conducted, so we are now, having done this analysis, we are  
24 starting to try to get as much information out of it as we

1 can, and that certainly is a very good question.

2 DR. LIPSKY: Certainly, you know, the definitions  
3 are important because we say treatment failure at an  
4 arbitrarily pegged value of limit of detection, when, in  
5 actuality, that limit of detection may be a treatment  
6 failure in and of itself, and it is just a question of what  
7 time will that unfortunate reality become apparent.

8 DR. QUART: Right. We are also looking at some of  
9 our stored samples with the ultra-sensitive PCR down to 50,  
10 as well, trying to evaluate that.

11 DR. LIPSKY: And it fits 10, and that changes  
12 things, too.

13 DR. QUART: Yes.

14 DR. HAMMER: Chris.

15 DR. MATHEWS: Two quick points. The first one is  
16 that treatment guidelines that have been proposed are used  
17 as a criterion for switching therapy, the one-month response  
18 and the value that is out in the literature is a 1-log drop,  
19 so for all of these presentations, I think it would be  
20 helpful to see like a 2 by 2 table that looked at the  
21 proportion of people who had either a 1-log drop or went to  
22 the limit of detection by four weeks compared to those that  
23 ultimately responded by the various criteria that you are  
24 using, because it is going to be hard to keep people in

1 trials if the switch points are inconsistent with practice  
2 guidelines.

3           Secondly, your conclusion that the CD4 response  
4 early should not be used as part of the definition of  
5 treatment failure, I would question because it seems to me  
6 the decision about whether or not you include CD4 should not  
7 be based on whether or not those same patients were durable  
8 virologic responders, but rather based on their prognosis  
9 for clinical events.

10           I think there was some data presented yesterday in  
11 the Glaxo presentation that suggested that patients who had  
12 virologic response, who did not have CD4 responses, had  
13 different event rates than those who had concordant  
14 responses.

15           DR. QUART: Right. I appreciate that. I may not  
16 have been completely clear. What I was trying to get across  
17 is that, in fact, CD4 count, at least we were surprised to  
18 find was much more variable in that period of time, and, in  
19 fact, those patients went up some, came back down to  
20 baseline, and then most of them went back up and continued  
21 to have a good CD4 count response, so in terms of their  
22 long-term prognosis, I would consider them a responder, yet,  
23 in the early period, they seemed to have more fluctuation of  
24 CD4 count.

1 DR. HAMMER: Fred.

2 DR. VALENTINE: On this same point, perhaps the  
3 committee would be less concerned about this, you commented  
4 that during the course of this study, when you went back and  
5 looked, the investigators had called failures as a  
6 consequence of CD4 changes, were there predetermined  
7 criteria by which CD4s were used to declare a failure, and  
8 how early--you emphasized early changes--how early was this  
9 going on, because if we are going to be waiting for 28 weeks  
10 to assess virologic responses, then, the same time period I  
11 would guess would be used for CD4.

12 DR. QUART: Right. Actually, these treatment  
13 failures were evaluated by a DSMB, and the criteria was as I  
14 described, a return to baseline of two consecutive values  
15 after four weeks of therapy, and where we saw most of the  
16 fluctuation was beyond four weeks and basically the second  
17 and third month of therapy, where there seemed to be a  
18 decline and then a return back up towards increases.

19 DR. VALENTINE: What happened subsequent to those  
20 CD4 measurements with switches or whatever was done?

21 DR. QUART: In these particular patients, they, in  
22 general, had a very good CD4 count response in terms of  
23 looking at the endpoint of 24 weeks of therapy, there was  
24 just early--in terms of early meaning the second month and

1 third month of therapy--there was a surprising amount of  
2 fluctuation.

3 DR. VALENTINE: And then it corrected itself.

4 DR. QUART: Yes, and I think it is possibly a  
5 certain assay variability, as well as virologic variability.

6 DR. HAMMER: Pamela.

7 DR. DIAZ: In the long-term responders who had  
8 their RNA values above the limits of quantification,  
9 particularly in those five individuals who had two  
10 consecutive measurements above the LOQ, and additionally, in  
11 the other 28 who had at least one measurement above, can you  
12 comment on them clinically in terms of was there something  
13 in particular in those five at that time, an intercurrent  
14 infection or some other clinical issue that might explain?

15 DR. QUART: That is a very good question and I  
16 suspect if we went back, we might be able to find that, but  
17 to be honest, I have not gone back in those particular  
18 patients to look at that period of time to see whether or  
19 not there was some intercurrent illness, but we have  
20 certainly anecdotally found patients who get immunizations  
21 or have intercurrent illness, have a brief period of where  
22 they have a rebound in viral load.

23 DR. HAMMER: Thanks very much.

24 I think we will move on. The next speaker is

1 David Hall from Boehringer Ingelheim.

2 [Slide.]

3 DR. HALL: I am going to be presenting a trial.  
4 Most of you have probably seen it presented before as the  
5 INCUS trial. It is a trial of triple therapy with  
6 nevirapine, ICDV and DDI compared to ZDV/DDI, and ZDV/  
7 nevirapine.

8 There is 150 patients in the trial. In this  
9 trial, viral load was the primary endpoint, and it was  
10 measured with the Amplicor assay initially, going to 400  
11 copies/mL as a lower limit of detection.

12 In patients who were below 500 copies/mL, the  
13 specimens were all retested using the Amplicor Ultra Direct  
14 which involves taking a larger specimen, processing it  
15 through ultra centrifuging and intensifying the signal that  
16 way, and getting down to 20 copies/mL.

17 The bulk of my presentation will be showing you  
18 how much difference there is between the result you see at  
19 20 copies and at 400 copies.

20 In this trial, on the triple therapy, the majority  
21 of patients made it below detection just because the trial  
22 was early on before compliance was a serious concern or  
23 recognized as a serious concern, and because the DDI was the  
24 initial formulation, there were tolerance problems and a

1 number of patients did not stick to their regimen daily.

2           This is the list of the participating  
3 investigators, the trials, an international trial in Canada,  
4 Italy, Australia, and the Netherlands.

5           [Slide.]

6           Again, as I said, it is a trial, placebo-  
7 controlled in naive patients with no clinical disease. They  
8 had to have over 200 CD4 cells and no AIDS-defining  
9 illnesses in their history. The trial design was to have  
10 every patient stay in the trial until the last patient  
11 completed 52 weeks of treatment. Primary endpoints were  
12 viral RNA and CD4.

13           [Slide.]

14           The baseline characteristics, we ended up with  
15 patients with a mean CD4 count of 376 cells ranging from 145  
16 to 755 at baseline, and the 145 at screening was above 200.

17           The mean viral load was 25,000--that is a  
18 geometric mean--25,000 copies/mL.

19           [Slide.]

20           The methods for the virology, the plasma was  
21 collected respectively with EDTA or ACD as an anticoagulant.  
22 The plasma RNA was measured, as I said, with the Amplicor  
23 PCR assay with a limit of quantification of 400. The  
24 labeled limit of detection is 200.

1           The Ultra Direct assay was used to improve the  
2 sensitivity on all the specimens that were below 500 copies.  
3 All assays were performed batched and blinded.

4           [Slide.]

5           This shows at both limits how the triple therapy  
6 arm did through time in percent of patients below the limit  
7 of detection. There is a big difference early. It is  
8 fairly clear that it takes quite a period of time to go from  
9 400 to 20. The peak at 20 is at 12 weeks, 16 weeks when 65  
10 percent had achieved the low limit of detection, while you  
11 have gotten to 75 percent by 4 weeks with a limit of  
12 detection of 400. I have a number of slides that show more  
13 of that pattern.

14          [Slide.]

15          This slide is a Kaplan-Meier curve of the time to  
16 below the limit of detection for the patients who made it  
17 below the limit, the 35 of 51 patients who went below the  
18 limit of detection at 20. As you can see, it took until 22  
19 weeks for all of those patients to get below 20. The median  
20 is 12 weeks.

21          [Slide.]

22          When we look at the 400 copies, the drop is very  
23 dramatic, very quick. By 4 weeks, 85 percent of those who  
24 made it below the limit of detection, 43 of the 51 had

1 achieved that limit.

2 [Slide.]

3 Just to facilitate the comparison, here is both  
4 lines on the same graph. So, in fact, we are getting an 8-  
5 week delay really, 8- to 12-week delay in getting to 20 as  
6 opposed to just getting to 400.

7 When we looked at baseline characteristics that  
8 might be related to the time looking at the 20 copy limit,  
9 baseline CD4 had a--there appears to be a difference in the  
10 middle here, however, the ones with the lower CD4 seemed to  
11 be taking longer, and we don't think this is a real  
12 difference.

13 [Slide.]

14 Again, this same pattern is seen a little less  
15 dramatically with the 400 copy limit. When we look at the  
16 RNA, the pattern is similar to what people have described  
17 before. It is sustained to the end of the period, and those  
18 with a higher RNA do take longer to get to the limit of  
19 detection.

20 [Slide.]

21 In this case the limit being 20, and in this case  
22 the limit being 400, it is clearly less dramatic here.

23 [Slide.]

24 Just to get a look at the patterns of the ones who

1 took 8 weeks or longer to get down, these are the patients  
2 who took 8 weeks. Our criteria for calling a patient a  
3 responder was simply one value down, and as you can see,  
4 there are a few blips up.

5           There is one of these patients who reached the  
6 limit at 8 weeks, who was not down for terribly long, but  
7 all but that one patient had no more than one, which doesn't  
8 qualify as failure, that rose above the limit of detection,  
9 and the majority of them stayed below through 6 months.

10           These patients tend to be slightly above the  
11 overall median, again supporting the pattern I showed before  
12 of the patients with higher baselines taking longer to get  
13 below detection.

14           [Slide.]

15           This is the group that reached the limit at 12  
16 weeks. Again, they are up to above 5 logs, the majority  
17 above 4. With this one exception, the little variations  
18 from monotonicity, the little rises here are well under half  
19 a log. They could very reasonably be considered measurement  
20 error, and the pattern in general is a consistent decline in  
21 these patients.

22           [Slide.]

23           The same is true here in the patients who took 16  
24 weeks and longer to reach the limit of detection. There is

1 a fair bit of noise here, but again, the majority of these  
2 are showing a fairly consistent pattern with perhaps one  
3 rise that is more than half a log, one would have trouble  
4 calling measurement error.

5 [Slide.]

6 The next thing we looked at was the time from that  
7 first response to a confirmed detectable criteria for  
8 failure were two consecutive values above the limit of  
9 detection. This shows for the triple therapy group for both  
10 limits of detection, the shape of this curve. Again, this  
11 is from the time of the first below detection, and there is  
12 a gradual decline to approximately 50 percent who, at 60  
13 weeks and more, were still below the limit of detection.

14 [Slide.]

15 When we looked at baseline characteristics, again,  
16 there is no sign here using the limit of detection of 20,  
17 looking at the baseline CD4 splitting at the median, there  
18 is no sign of the baseline CD4 having any predictive value  
19 for the time to failure here.

20 [Slide.]

21 The same is true with the limit of detection of  
22 400.

23 [Slide.]

24 When we look at the RNA, it is a very dramatic

1 pattern. The patients with greater than the median fail at  
2 a fairly dramatic rate, and the ones with less than the  
3 median, which was 4.18, sustained their response very well.  
4 This is the less than 20.

5 [Slide.]

6 This is the 400. With the 400, there isn't much  
7 during the first six months, but they separate dramatically  
8 after six months.

9 [Slide.]

10 Looking at the time to first response in terms of  
11 whether that turns out to be a factor, given that it was  
12 related to the baseline, the baseline RNA level, one would  
13 expect there to be some relationship, and there is a weak  
14 relationship with the longer term ones who had higher  
15 baselines declining a bit more rapidly, but the difference  
16 is not very large and I think we would interpret it as being  
17 just due to the confounding with baseline level.

18 This is one is the median for the 400 group, was  
19 two weeks, but again, the difference is not very large, and  
20 I think it is really due to the difference between the ones  
21 who take longer to respond having a higher baseline RNA  
22 level, and that would be the basis for this more rapid  
23 decline.

24 [Slide.]

1           In looking at the patients who failed, we wanted  
2 to get some sense of what happened to them after they were  
3 confirmed failures. This is a very noisy slide, but I think  
4 the message is fairly simple.

5           Here, we showed what their baseline levels were,  
6 so you could get a sense of whether they are returning back  
7 to their baseline. This is their last observation below the  
8 limit of detection, usually at 4 weeks before the visit at  
9 which they first failed.

10           The pattern is, in general, for them to rise  
11 fairly. They might blip up, they tended to come back down a  
12 little if they did, and rises were fairly gradual. The  
13 great majority of patients did achieve levels well above 3  
14 logs above 1,000 copies, and again, the majority of them  
15 stayed up there having reached that level.

16           [Slide.]

17           This is looking at the patients who--and that  
18 first one was the subgroup of patients who were below the  
19 median RNA level among the failures, so these started with a  
20 lower baseline.

21           When they failed, there is one here, the light  
22 blue line, whose failure was a rise to just a little above  
23 100 copies, who did return to below detection at a second  
24 time of a similar pattern of two values above the limit of

1 detection, and then went back down, but that is the only  
2 patient with that pattern. In general, the pattern in these  
3 patients was to return--with these ones with fairly low  
4 baselines--to return to approximately their baseline levels.

5 [Slide.]

6 The third area we wanted to look into, we wanted  
7 to look at the relationship between how well response was  
8 sustained and what the best response was. So this is a  
9 graph across the x axis, is the lowest achieved level of HIV  
10 RNA and then on the y axis is the number of weeks that these  
11 patients stayed within one-half log of that nadir, and as  
12 you can see, the pattern is very dramatic.

13 If they did not achieve the limit of 20 copies,  
14 and I will point out all of these and actually a few of  
15 these are less than the 400 copy limit, they were not able  
16 to sustain a response at all. This is for the triple  
17 therapy arm.

18 [Slide.]

19 This is the same figure for the double therapy  
20 arm. Again, the pattern is quite similar. If you got to  
21 20, you were able to sustain a response for up to a year  
22 after, and most of these are censored, they didn't actually  
23 fail at this time, it's just the last observation, but if  
24 you did not achieve below 20, and all of these are below

1 400, then, your duration of response was on the order of 8  
2 weeks.

3 [Slide.]

4 Looking at this in terms of the Kaplan-Meier  
5 curve, the solid line is the group from both of these two  
6 treatment arms who made it to less than 20 copies, and the  
7 other line is all those who were greater than 20 copies. I  
8 think the difference between the two lines speaks for  
9 itself.

10 [Slide.]

11 We tried to look at the same question one  
12 additional way. We took our definition of failure as rising  
13 to within one log of baseline. Again, on those previous  
14 figures, it was staying within a half a log of the minimum.

15 When we used a criteria of failure in terms of the  
16 result relative to baseline, the figure is similar. The  
17 message is pretty clear even like this. [Slide backwards.]

18 The yellow line is the Kaplan-Meier--for those of  
19 you who like to read right to left--of the people who are  
20 less than 20, and the blue line is the people who are  
21 between 20 and 400, and they are virtually identical to the  
22 people who were greater than 400, so the message here is  
23 that the return to baseline is the same for the group of  
24 patients here who made it to below 400, but not 20, who made

1 it to nondetectable by the readily available assays, and the  
2 curve is dramatically different for those who made it to  
3 below 20, to below detection by the Ultra Direct assay.

4 [Slide.]

5 In conclusion, the time to suppression was clearly  
6 associated with the baseline viral load, and could be as  
7 long as 6 months, the time to getting below 20 copies. The  
8 limit of detection at 400 copies underestimated the time to  
9 full suppression by 8 to 12 weeks when compared to 20.

10 At least through the 20 copies, less than full  
11 suppression is associated with transient suppression at  
12 least in this trial, and confirmed failure to sustain plasma  
13 virus below 20 copies was usually associated with a return  
14 to at least above 1,000 copies/mL.

15 That is the end of my talk.

16 DR. HAMMER: Thank you very much.

17 Are there questions for Dr. Hall? Jim.

18 DR. LIPSKY: Based on what you have showed us, are  
19 you abandoning a 400-copy limit of detection?

20 DR. HALL: Certainly, in our trials we are trying  
21 to reassay all the specimens to get down lower, and, yes,  
22 would want to do that in all future trials.

23 DR. HAMMER: Do you want to comment on perhaps the  
24 triple therapy with an NNRTI versus a triple therapy with a

1 protease inhibitor, because we heard Jeff allude to the fact  
2 that with some bouncing around, around the 50 copy/mL level  
3 in 035, there were still more persistent suppression here.

4 Here, it looks like if you bounce around above the  
5 20 to 50 copy range, you are losing it.

6 DR. HALL: I think that is actually a comparison  
7 of apples and oranges.

8 DR. HAMMER: It is.

9 DR. HALL: But I don't think it is in the  
10 treatments. What they did with looking at the 50 limit was  
11 to test at least four different specimens, four replicates,  
12 and to call it a positive if any one of those four was  
13 positive.

14 Brian Conway, who did the virology in our trials,  
15 also used some larger volume specimens and found that he  
16 could usually find virus if he looked harder, so that, in  
17 fact, they are less than 20s, but they are definitely not  
18 zeros typically, and it is kind of a question of Poisson  
19 sampling whether a single value comes out positive.

20 DR. HAMMER: What about the nevirapine resistance  
21 that is coming up in the 20 to 400 copy/mL group, that  
22 doesn't sustain--

23 DR. HALL: What we have been able to look at so  
24 far has been six-month specimens. What we saw there was in

1 the patients who were below 20, from whom virus could be  
2 cultured, the virus was wild type. We tried to look  
3 phenotypically using Virco's assay. That required them to  
4 get up as high as 1,000, and if they had gotten that high,  
5 they always had resistant virus.

6 DR. HAMMER: Thank you. Joel.

7 DR. VERTER: I wonder if you could just clarify.  
8 In the three groups, how many were in each group, and what  
9 percent were responders in each of the groups?

10 DR. HALL: What percent were responders in terms  
11 of getting below the limit of detection - I do have a slide  
12 for that. I hope it is facing the right way. In general,  
13 if you went to the less than 20, with less than 20, two-  
14 thirds of the triple patients were responders.  
15 Approximately 40 percent of these ZDB/DDI patients were  
16 responders, and less than 10 percent of the ZDB/nevirapine  
17 patients ever responded, and theirs was not sustained at  
18 all.

19 DR. HAMMER: And there is about 50 patients in  
20 each arm?

21 DR. HALL: Right.

22 [Slide.]

23 This shows the general pattern of the virology.  
24 The ZDB/nevirapine patients had a very transient response,

1 and there were only I believe five of them who ever achieved  
2 below the limit of detection. They were all patients with  
3 very low baselines.

4           The triple therapy had more than a 2-log drop, and  
5 again, two-thirds of them achieved below the limit of  
6 detection and approximately 40 percent of the ZBD/DDI  
7 patients achieved below the limit of detection.

8           DR. HAMMER: Other questions? Mark.

9           MR. HARRINGTON: Could you put up figure 13 again,  
10 because I want to ask a question about clinical management.  
11 I mean I am wondering whether people are getting the  
12 impression that we need the more sensitive assay for  
13 clinical management, and what I took away from figure 13 was  
14 that you might as well use the commercial assay because you  
15 are going to come back up above 400 anyway if you are  
16 between 20 and 400. Is that right? Is this the figure?

17           [Slide.]

18           DR. HALL: Yes, that's it. That is what this  
19 would suggest, that the ones between 20 and 400 will come  
20 up. Yes, so if you are just tracking the patient for  
21 clinical care, unless you were going to switch very quickly  
22 when they failed to achieve 20, I am not sure how you would  
23 decide they had actually failed while they were still down  
24 between 20 and 400, so, yes, I think you are right for

1 clinical care, the 400 is probably fine.

2 DR. HAMMER: Thank you very much.

3 The last presentation is by Ralph DeMasi and Lynn  
4 Smiley from Glaxo Wellcome.

5 DR. SMILEY: Thank you, Scott.

6 [Slide.]

7 Again, we appreciate the opportunity to present  
8 today. Let me refer the committee to the copy of our slides  
9 for today that is included with yesterday's packet.

10 After some brief introductory comments, Ralph  
11 DeMasi will present our results and conclusion.

12 [Slide.]

13 The data we are going to present today are from a  
14 cross protocol analysis done that included approximately  
15 1,100 patients on six prospective randomized, double-blind  
16 clinical trials including the CAESAR study, which as most of  
17 you remember is our adult clinical endpoint study, the 3001  
18 trials which were surrogate marker trials in less advanced  
19 HIV-infected individuals that were naive to antiretroviral  
20 treatment, the 3002 trials were two trials conducted in  
21 treatment experienced population, and the AVANTI-01 trial is  
22 a trial of ZBD/3TC versus a triple combination including an  
23 investigational NNRTI.

24 These were the six studies sponsored by Glaxo

1 Wellcome conducted and completed within the past two, two  
2 and a half years. The treatment duration was typically for  
3 one year, and we measured RNA using the Roche Amplicor  
4 assay.

5 [Slide.]

6 The data you are going to see today are an on-  
7 treatment analyses on responders, and responders were  
8 defined as those who reached below detectability, which is  
9 at a cut point of 400, and we also looked at 5,000, and it  
10 was those who had one viral load value at that level.

11 The loss of response was defined as two  
12 determinations above the limits of detection.

13 So, as mentioned, we looked at time to  
14 undetectability, time to reappearance or loss of response,  
15 stratified by baseline CD4 and RNA, and again looked at the  
16 two different cut points below 400 and below 5,000.

17 Cox models were used for multivariate analysis to  
18 examine the effects of baseline CD4 and viral RNA.

19 Our population was predominantly male, mean age  
20 37, and about half the patients were naive and half the  
21 patients were experienced naive defined as less than 6  
22 months of prior therapy.

23 [Slide.]

24 This shows the mean baseline RNA, which is similar

1 to the intent-to-treat population at about 63,000 copies/mL  
2 at 4.8 log and baseline mean CD4 of about 202, so about two-  
3 thirds of our patients were above 50,000 copies/mL.

4 I will go ahead and turn it over to Ralph.

5 [Slide.]

6 DR. DeMASI: Before we get into addressing some of  
7 the questions that some of the other groups have presented  
8 today, I just wanted to indicate the number of evaluable  
9 patients by time of study.

10 The y axis here is just the number of patients  
11 that have RNA values while on treatment, and as Lynn said,  
12 this is an on-treatment responders' analysis, and the x axis  
13 here is the number of weeks on study, and this indicates  
14 that we had approximately 1,100, as Lynn mentioned, at  
15 baseline, and then as the study progressed, we see fewer  
16 number of patients remaining, but nevertheless, we still  
17 have over 100 patients of the less than 6 months prior  
18 treatment and greater than 6 months prior treatment treated  
19 patients evaluable at about 24 to 52 weeks of treatment.

20 [Slide.]

21 I realize that this is a little hard to see with  
22 the different lines here, so I am going to do my best to  
23 trace out the profiles. Once again, here, I am just trying  
24 to indicate some of the additional characteristics of the

1 antiretroviral response to AZT/3TC, and what we have here is  
2 a median change from baseline and log RNA.

3 On the y axis here is the log change, the x axis  
4 is the weeks on study, and what we can see here is that the  
5 pink line represents patients who had less than 6 months  
6 prior therapy, and the green line is patients who had  
7 greater than 6 months prior therapy.

8 What we can see is a good early antiretroviral  
9 effect, particularly for the less than 6 months of prior  
10 pretreated patients. We see about a 2-log reduction  
11 relative to about a 1 1/4-log reductions for the greater  
12 than 6 month pretreated patients.

13 Furthermore, we can see a classical AZT/3TC  
14 response for the two groups in that we see a slight lack of  
15 response or loss of response after about 8 weeks, a gradual  
16 return to baseline, but nevertheless, we see a sustained  
17 reduction to about 1 to 1.5 log for the naive subset and  
18 about 0.5 log for the experienced subset.

19 [Slide.]

20 This is one overhead that is not in your briefing  
21 package, but I wanted to include it. It reflects on some of  
22 the issues that were brought up yesterday in terms of  
23 looking at the different metrics of RNA response.

24 What I have done here is to correlate the 16- and

1 24-week median change from baseline on the log scale for  
2 each treatment arm in the particular studies that were  
3 included in yesterday's and today's presentations.

4           So what we have here on the y axis is the 24-week  
5 change from baseline on the log scale. On the x axis is the  
6 16-week change from baseline. Each particular point  
7 represents a treatment arm in the studies that were  
8 included, and what we can see here is that the size of the  
9 point represents a relative magnitude of the treatment arms  
10 in terms of the number of patients evaluable for RNA.

11           What we see here, then, is an excellent  
12 correspondence between the 24-week change from baseline and  
13 the 16-week change from baseline. In particular, we can  
14 note that there is a very linear relationship here. The  
15 line of equality would actually run from zero down to--this  
16 is a 2-log reduction here. So you can see a slight loss of  
17 effect between 16 and 24 weeks, but nevertheless, a very  
18 good correspondence between the two metrics.

19           [Slide.]

20           Now, I would like to turn to addressing some of  
21 the questions mainly for today's presentation about the  
22 initial virologic response and then subsequently, we will  
23 look at the loss of virologic response.

24           This first analysis that we will be looking at is

1 the initial response, and it is the time to less than 400  
2 copies/mL. Actually, I would like to focus your attention  
3 on this part of the figure.

4 This gives the percent of patients that had  
5 achieved complete undetectability at anytime during the  
6 study, so less than 400, and it is broken down again by the  
7 different subgroups, the patients that had less than 6  
8 months prior therapy and the patients who have had greater  
9 than 6 months prior therapy.

10 So what we can see here is that 45 percent of the  
11 patients with less than 6 months prior therapy achieved 400  
12 copies/mL at anytime during the study, compared to about 19  
13 percent of the pretreated patients.

14 [Slide.]

15 Now, I would like to turn to the two lines here  
16 that I have shown on this plot. This is the 1 minus, the  
17 Kaplan-Meier estimates of the time to virologic response.  
18 So on the y axis here, we have the proportion of patients  
19 that have achieved a virologic response of 400 copies/mL,  
20 and on the x axis, we have the time on study.

21 So what we can see here is that the majority of  
22 patients that actually achieved the 400 response do so  
23 between, say, 8 and 12 weeks, in particular, the percents  
24 are between 80 and 90 percent.

1           Once again, these lines are just for the patients  
2 who have achieved this response during the study, so it is  
3 the subset of patients.

4           [Slide.]

5           Now, I would like to show you the effect of the  
6 baseline RNA on the ability or capacity to achieve such a  
7 response of 400 copies, and we are looking here at subjects  
8 with less than 6 months of prior therapy.

9           Once again, this table here and the figure, the  
10 insert indicates the particular strata that were used to  
11 stratify patients on baseline RNA, and then the numbers here  
12 indicate the percent of patients that achieved the limit of  
13 400 or the percent of those patients.

14           So we have the limit. The ranges are patients  
15 that had baseline RNA less than 5,000, 5- to 20,000, 20- to  
16 50,000, 50- to 200,000, and greater than 200,000. What we  
17 can see here is a much higher likelihood of patients who  
18 start at the lower RNA level, say, less than 5,000 or 5- to  
19 20,000, to actually achieve this undetectability of viral  
20 load at anytime during the study. In particular, the  
21 percents were about 90 percent.

22           Furthermore, we can see a diminishing, a gradient  
23 of response, and the patients who started out greater than  
24 200,000, only 9 percent of those achieved 400 copies/mL at

1 anytime during the study.

2           Now, for these patients who actually achieved this  
3 response, these curves give the distribution of the times  
4 that it took to achieve such a response of 400, and once  
5 again, here, we have split out the groups by the particular  
6 RNA stratum at baseline, so the yellow again is less than  
7 5,000, 5- to 20-, 20- to 50-, 50- to 200-, and greater than  
8 200.

9           What we can see from this display is for patients  
10 who started out with lower baseline RNA, it took them a  
11 shorter time to achieve this response of 400 copies than  
12 patients who started with a higher baseline RNA, and that  
13 there is a gradient of effect in between the lowest and  
14 highest strata.

15           [Slide.]

16           This is the same display for patients with greater  
17 than 6 months prior therapy, and once again, we have the  
18 same, the strata that were used, 5,000, 5- to 20-, et  
19 cetera, and these percentages indicate the percent of  
20 patients that achieved the 400 at anytime during the study,  
21 and we note that approximately 75 percent of the patients in  
22 the lower stratum achieved the response of 400, and that  
23 actually, none of the patients in the stratum greater than  
24 200,000 achieved that response on study.

1           Then, if we look at the time to such a response,  
2 we can see that the lower three strata are essentially  
3 superimposable, but the patients who start out at 50 to  
4 200,000 had slightly longer times to reach the limit of 400,  
5 and there are only 6 percent of the patients in this  
6 particular stratum.

7           [Slide.]

8           I would now like to turn to looking at the  
9 likelihood of initial virologic response in terms of the 400  
10 copy/mL, so complete undetectability in terms of predicting  
11 that likelihood based on baseline covariates, such as the  
12 baseline RNA, CD4 count, and prior therapy

13           .

14           What we found is that these are the hazard ratios  
15 for achieving this response for a 1-log reduction in RNA or  
16 a 50-cell increase in CD4.

17           What we can see, these are the p values for  
18 testing the null hypothesis that this hazard ratio is 1, and  
19 we can see that patients with lower RNA values, those that  
20 have less than six months prior therapy, are about 4 times  
21 more likely to achieve this response of 400 copies/mL than  
22 other patients.

23           The effect of baseline CD4 count here was  
24 marginally significant with a p value of about 0.08.

1 [Slide.]

2 I am going to give the conclusions for each data  
3 presentation as I go along, and in conclusion, for the  
4 initial reduction to under 400 copies/mL, we have noted that  
5 approximately 90 percent of the patients who become  
6 undetectable do so within the first 12 weeks.

7 Furthermore, this occurs in the higher proportion  
8 of naive patients than pretreated patients, and it is more  
9 likely and occurs sooner for patients with lower RNA and  
10 also this higher CD4 count was borderline significant.

11 [Slide.]

12 I would now like to turn to the loss of response.  
13 Once again, this is a responders' analysis. What we did is  
14 we looked at the time to detectable RNA, so this is a  
15 rebound to above 400 copies/mL, and this was restricted to  
16 the patients who had achieved the 400 copies on treatment,  
17 and what we have done here is just split out the analysis by  
18 the two subgroups of patients with greater than 6 months in  
19 the green line here, and then less than 6 months' prior  
20 therapy in the pink line here.

21 What we can see is that, in general, there is a  
22 slight difference here in the less than and greater than 6  
23 months' prior therapy, but whether or not this is clinically  
24 meaningful is not addressed here.

1           There is about 50 percent of the patients who  
2 actually have a durable response as measured by this cut  
3 point of 400 at 52 weeks.

4           [Slide.]

5           Now, what we have done is we have split this out  
6 by baseline RNA and once again we have the same strata, the  
7 5, less than 5,000, 5- to 20- in the blue, 20- to 50- in the  
8 red, and 50- to 200- in the dark blue.

9           What we can see here, this is for patients with  
10 greater than 6 months' prior therapy, and we can see this  
11 gradient of effect between patients having lower RNA values  
12 having a more durable response than patients having higher  
13 RNA values at baseline.

14          [Slide.]

15          This is the same presentation split out for  
16 patients that have less than 6 months' prior therapy. Once  
17 again, here, we can see the gradient of effect. Patients  
18 with lower RNA values have a more durable response in  
19 general than patients with higher RNA values.

20          [Slide.]

21          This is a similar analysis looking at the risk of  
22 RNA rebound or increase above 400 copies, and the predictors  
23 that we are looking at again are baseline RNA, baseline CD4  
24 count, and less than 6 months' prior experience.

1                   We have the hazard ratio here for risk of increase  
2 above 400 copies for a 1-log reduction and for patients who  
3 have less than 6 months' prior experience, and we can see  
4 that those two, the RNA and the prior experience, are  
5 statistically significant, and, in fact, those patients have  
6 a more durable response as indicated in the previous  
7 overheads.

8                   [Slide.]

9                   In conclusion, we have seen that approximately 50  
10 percent of patients have a loss of response above 400 at 6  
11 months. This occurs in a slightly higher proportion of  
12 pretreated patients than naive patients, and the loss of  
13 response is more likely and occurs sooner for patients with  
14 higher baseline RNA.

15                   [Slide.]

16                   I would now like to turn to answering the question  
17 of whether or not patients who achieved undetectable levels  
18 on treatment have a more durable antiviral response, and  
19 this durability of response is measured by the time or the  
20 likelihood of remaining within 0.5 log of the lowest RNA  
21 level achieved, which is defined as the nadir.

22                   We looked at similar methods of Kaplan-Meier  
23 analyses, and the actual strata that we used are patients  
24 who have achieved undetectability of 400, between 400 and

1 1,000, and 1,000 to 5,000.

2           Then, we are looking at the time to first RNA  
3 rebound above 0.5 log of the nadir.

4           [Slide.]

5           This first presentation is for patients who have  
6 had less than 6 months' prior treatment, and what we can see  
7 here is that the yellow line is the patients who have  
8 achieved less than 400 on treatment, the cyan is for  
9 patients who achieved 400 to 1,000, and the red is for  
10 patients who achieved 1,000 to 5,000.

11           So what we can see here for the naive subset is a  
12 gradient of effect again between the patients who have  
13 achieved complete suppression, having a much more durable  
14 response than patients who have achieved good levels of  
15 suppression, low levels, but still not complete  
16 undetectability.

17           [Slide.]

18           Now, this is the same analysis for the experienced  
19 subset, and what we saw here was that there actually was a  
20 slight difference early on, but then this difference was no  
21 longer significant, so this would indicate for patients who  
22 have more than 6 months of prior therapy, that this  
23 relationship between the actual level achieved and the  
24 durability of effect did not hold, but I would like to

1 caution, some of the interpretation of this display, based  
2 on the low numbers of patients achieving undetectability for  
3 the pretreated group and also the fact that this may reflect  
4 a particular resistance profile of AZT/3TC.

5 [Slide.]

6 In conclusion, during the 52-week interval of  
7 AZT/3TC treatment, a subset of patients with under 6 months  
8 of prior treatment, whose RNA values fell to under 400  
9 copies, had reductions sustained to within 0.5 log of their  
10 nadir, and that the pretreated patients greater than 6  
11 months are those with nadir levels that did not reach  
12 complete undetectability, did not sustain their RNA levels  
13 within 0.5 log of their nadir.

14 I would now like to turn to the last presentation,  
15 and this tries to answer the question of whether or not  
16 patients who lose maximal suppression can subsequently  
17 remain virologically stable.

18 [Slide.]

19 What we did in this analysis, if patients' viral  
20 load increases 0.5 log above the lower limit of 400, what is  
21 the likelihood of remaining below 5,000 copies per mL at a  
22 certain time period later.

23 For this analysis, we looked at--we restricted  
24 this analysis for patients who started out 0.5 log above

1 5,000 and who actually achieved 400 copies/mL, and then the  
2 time zero was the time at which they failed, that means  
3 going above 400 copies, and then we looked at the time that  
4 they remained below 5,000 copies, so virologically stable by  
5 this definition of 5,000.

6 [Slide.]

7 So the results here are what we found. The green  
8 line is for patients who had less than 6 months of prior  
9 therapy, the pink line is for patients who had greater than  
10 6 months of prior therapy, and this gives the proportion  
11 remaining stable at particular time points after they have  
12 lost the virological response of 400, so after they are  
13 considered to be failed on the 400 criterion, and this  
14 really indicates that patients who are classified as having  
15 failed on the 400 criterion, about half of those patients  
16 remain virologically stable in the sense that they have RNA  
17 values below 5,000, which was actually less than their  
18 baseline value which could be considered their setpoint  
19 prior to entry into the study.

20 [Slide.]

21 In conclusion, approximately half of the patients  
22 remained stable, that is, less than 5,000, 6 months after  
23 rebounding above 400, and the experienced patients are  
24 slightly less likely to remain stable following the initial

1 rebound above 400.

2 That concludes the presentation.

3 DR. HAMMER: Thank you. Fred.

4 DR. VALENTINE: The same question you asked  
5 previous speakers, Scott. Do you have any genotypic  
6 resistance or phenotypic resistance data on this last group  
7 of patients who seemed to be hanging in there with a "new"  
8 setpoint?

9 DR. DeMASI: I think that is an excellent question  
10 and one of the things that we are continuing to look is the  
11 AZT/3TC resistance pattern, both the genotypic and  
12 phenotypic. In terms of this subset of patients, we have  
13 not looked at that.

14 DR. VALENTINE: The other, even more difficult  
15 assay that might shed light on this question is some way of  
16 measuring replication rates or fitness even if these viruses  
17 are not resistant. Why are they doing this, in other words?

18 DR. DeMASI: I am sorry, could you--

19 DR. VALENTINE: A measurement not only of  
20 resistance, but a measure of fitness for replication, too,  
21 might be telling in explaining this phenomenon.

22 DR. HAMMER: Mark.

23 MR. HARRINGTON: I just want to clarify something.  
24 If I read the data right, it suggested that 70 percent of

1 the responders who were AZT experienced were failures by 16  
2 weeks by the 400 assay, and that indicates that for most AZT  
3 or nucleoside experienced patients, the treatment response  
4 period is very brief for AZT and 3TC.

5 Does that mean that the company is not going to  
6 use AZT and 3TC as a control arm in the ongoing studies of  
7 its new compounds, 1592 and 141?

8 DR. DeMASI: I think that Dr. Smiley can address  
9 this question.

10 DR. SMILEY: Those patients in those studies are  
11 naive, and I think you asked the questions with respect to  
12 experienced. We looked at the data pretty thoroughly, as  
13 Ralph has presented, to look at what the treatment response  
14 is likely to be over 16 weeks, and also to balance what we  
15 need to do to ascertain or evaluate what a new drug brings  
16 into a combination, what it adds, both safety, tolerability,  
17 and efficacy.

18 We also know that in the design of our trials  
19 post-16 weeks is we monitor viral load, that the therapies  
20 they will have access to should drive them below detectable  
21 if they are not responding in the control arm.

22 MR. HARRINGTON: I didn't get a clear answer. Are  
23 there control arms using AZT and 3TC alone?

24 DR. SMILEY: Yes, in our superiority trials, we

1 have AZT/3TC for a 16-week duration.

2 MR. HARRINGTON: I would submit that that is  
3 outrageously unethical and you are driving people into 3TC  
4 resistance.

5 DR. SMILEY: Well, if we, Mark--

6 MR. HARRINGTON: Which may lead to 1592  
7 resistance.

8 DR. SMILEY: If we can agree to disagree, I think  
9 it is ethical as we do--

10 MR. HARRINGTON: As a community representative, I  
11 don't think I can agree to disagree. I think I have to  
12 demand that you change your study designs, and the FDA, as a  
13 protector of the public health, should not allow such  
14 designs in 1997.

15 DR. HAMMER: I think the point has been very  
16 clearly made for study design issues for your new drugs, but  
17 what we are talking about here is RNA as an endpoint, so if  
18 I can just ask the panel if there are any more questions for  
19 Dr. DeMasi or Dr. Smiley. Judith, and also we can open this  
20 up now for the next few minutes to questions to any of the  
21 speakers in this session.

22 DR. FEINBERG: Lynn or Ralph, since at least for  
23 some or many of the trials for these analyses, clinical  
24 endpoints were ascertained. Do you have any correlation or,

1 for example, the subset of people who rebounded, but  
2 maintained what you had defined as virologic stability, less  
3 than 5,000 copies, do you have any clinical correlates for  
4 any of these subsets?

5 The other question is, Ralph, how many patients  
6 are in this subset, which it is not easy to divine from the  
7 data you have given us? In other words, there is  
8 proportions, but there is no n's.

9 DR. DeMASI: Yes, actually, as part of the  
10 presentation materials from yesterday, we did some analyses  
11 looking at a virologic endpoint, a virologic failure, and  
12 then correlated that with a clinical progression, and it was  
13 shown that most of the patients that have virologically  
14 failed, it was 95 to 97 percent had actually gone on or had  
15 a concurrent clinical progression during the followup  
16 period.

17 DR. FEINBERG: But I mean specifically this subset  
18 that met these specific defined criteria of being above 400  
19 copies, but less than 5,000, this last part of the  
20 presentation where you have got a group of patients that you  
21 think are virologically stable, not some disastrous  
22 virologic state. Is there a clinical correlation for this  
23 subset, and how big is this subset?

24 DR. DeMASI: The clinical correlation for this

1 subset, we actually have not done that, but the patients  
2 who--there are only seven patients that progressed without a  
3 virological failure, and the size of the subset, the numbers  
4 should have been printed on the briefing package.

5 DR. FEINBERG: Oh, I see, it's the little numbers.  
6 It's hard to see them.

7 DR. DeMASI: One of the things that I did want to  
8 mention is that for some of these groups and we look at a  
9 52-week time period, that some of the numbers--and that is  
10 one of the reasons for including these in your package--fall  
11 off dramatically, between 24 or, say, 28 and 52 weeks.

12 I realize that is a little hard to read. At 6  
13 months there were 13 patients in the experienced arm and 45  
14 patients in the naive subgroup.

15 DR. HAMMER: Let me ask a question that harkens  
16 back to Winston Cavert's presentation yesterday. Do you  
17 have lymphoid tissue data and also the same question for  
18 David Hall, from the INCUS trial, on the patients who were  
19 suppressed on AZT/3TC below 400 copies, or the patients in  
20 the INCUS trial, well suppressed as far as what the lymph  
21 nodes look like as far as RNA suppression? What we see in  
22 the plasma may not always reflect what is in the lymphoid  
23 tissue with different levels of potencies of regimens.

24 DR. DeMASI: For this data set, we do not have

1 that data for these patients.

2 DR. HAMMER: Do you have it on any ACT/3TC well-  
3 suppressed patients? There are some data, of course, in  
4 dual nucleoside that Joe Wong presented at the Retrovirus  
5 conference.

6 DR. DeMASI: The data presented yesterday by  
7 Winston Cavert included the NUCB 2019, which was AZT/3TC,  
8 and then AZT/3TC/ritonavir, so we do have that data in which  
9 we have the viral load in different compartments, but in  
10 terms of strictly AZT/3TC, we do not have that.

11 DR. HAMMER: David, is that any INCUS trial  
12 lymphoid tissue data?

13 DR. HALL: All of the data from the INCUS trial,  
14 the lymphoid tissue work was done in patients after they had  
15 been at least a year on trial, and they all were below 20  
16 copies, and the virus in the lymphoid tissue was also  
17 clearly suppressed. It has been presented at meetings, I  
18 don't have it here.

19 DR. HAMMER: I have seen some of that, but I just  
20 sort of thought for the group it would be worth bringing  
21 that out, as far as the level of RNA expression that is  
22 suppressed in the lymphoid tissues.

23 DR. HALL: I am afraid I don't have any detailed  
24 information.

1 DR. HAMMER: Wafaa.

2 DR. EL-SADR: I think this is for Dr. DeMasi, but  
3 for others, as well. I mean from your curve, it shows the  
4 number that as you go along in the study, there is a marked  
5 drop in the number of individuals in whom you have HIV RNA  
6 values.

7 DR. DeMASI: The bar charts?

8 DR. EL-SADR: The bar charts. I am just wondering  
9 whether--I mean obviously, these people remained in the  
10 clinical trial. They were probably coming for--you had some  
11 clinical data on them, yet, somehow you were not able or the  
12 investigators did not obtain the HIV RNA levels, so I am  
13 just curious as to how, if we are moving towards or we think  
14 we are moving towards HIV RNA as an endpoint, what is the  
15 threat to us sort of having so many lost endpoints  
16 essentially as we move away from the clinical endpoint to  
17 more of the laboratory endpoint studies.

18 DR. DeMASI: One of the reasons you see the  
19 falloff in the number of patients with RNA values after 24  
20 weeks is because this was pooled data over several trials,  
21 and the B-3001 and 2 studies were actually 24-week surrogate  
22 marker trials that were trials for 3TC submission, and then  
23 the A-3001 and 2 trials were longer studies, but they were  
24 amended for a 24-week duration although we did have longer

1 term followup, and then the B-3007 trial, much of the RNA  
2 data, we had two RNA subsets.

3 We took a random sample of patients to  
4 retrospectively analyze the RNA values from that subset, and  
5 for those patients we just looked at data up to 28 weeks  
6 because we are interested in that subset to correlate the  
7 28-week changes with subsequent progression, and that is  
8 some of the data that was presented yesterday.

9 But in terms of whether or not the data sets that  
10 we presented here are representative from our trials, we  
11 have done comparative analyses looking at the RNA subset  
12 versus all other patients not included in the RNA subset,  
13 and there seemed to be very good correspondence between  
14 those two subsets.

15 DR. EL-SADR: At baseline, correspondence at  
16 baseline.

17 DR. DeMASI: Well, at baseline and in terms of  
18 response of treatment. The response, the RNA response and  
19 the CD4 response for patients remaining in the study was  
20 similar to those who dropped out early. There are several  
21 analyses that were presented as part of the 3TC submission  
22 and looking at the effect of withdrawals on the treatment  
23 comparisons, the basic 3TC versus the control regimens in  
24 those trials.

1 DR. HAMMER: Thank you very much. Let's take a  
2 15-minute break and return just after 10:15.

3 [Recess.]

4 DR. HAMMER: Let's reconvene.

5 Dr. Elashoff, Division of Antiviral Drug Products,  
6 will provide a summary to us in advance of the open public  
7 hearing.

8 **Summary**

9 [Slide.]

10 DR. ELASHOFF: The reason we asked for this data  
11 was to aid the committee in the design of an RNA-based  
12 clinical trial. We are focusing on time to loss of response  
13 as the primary endpoint of these studies.

14 I will be discussing RNA, but this endpoint may  
15 also include clinical endpoints and CD4 endpoints, as well.  
16 The advantage of this design is that subjects can switch  
17 when they reach an endpoint, and the analysis is not  
18 complicated by dropouts, treatment changes, and subjects are  
19 not asked to stay on ineffective regimens.

20 Subjects should also be able to switch if no  
21 response was achieved in the first place. This summary will  
22 discuss the timing of this decision. Finally, an RNA trial  
23 could perform double duty in that the initial phase of the  
24 trial could be used for accelerated approval on the basis of

1 percent response and the long-term followup would address  
2 the durability of the drugs.

3 [Slide.]

4 Several questions must be answered to design the  
5 long-term RNA clinical trial - what is a response, what is a  
6 loss of that response, how long should subjects be kept on  
7 initial therapy while waiting for a response, how long  
8 should these trials be, and do the answers to these above  
9 questions depend on the populations studied?

10 [Slide.]

11 This is just an overview of the studies presented  
12 earlier.

13 [Slide.]

14 So to answer these questions, we asked the  
15 companies to look at some specific aspects of RNA behavior  
16 in their trials. Basically, there are three phases for RNA  
17 during the course of these studies: the initial decline to  
18 some low level, the time spent at or near that low level,  
19 and then the inevitable increase.

20 We are interested in the timing of each of these  
21 three phases, as well as the relationship of these three  
22 phases to each other, and how these phases are impacted by  
23 different baseline populations.

24 [Slide.]

1           For an initial RNA response, we focused on  
2 achieving the lower limit of the assays. In these studies,  
3 that was certainly an achievable goal although in more  
4 advanced populations a less stringent requirement may be  
5 necessary.

6           [Slide.]

7           The lower limits that were used in the  
8 presentations were 1,200 for the bDNA, 4- or 500 for the  
9 PCR, and 20 to 50 for the more sensitive PCR assay. Both  
10 Boehringer and Merck analyzed some of their data using both  
11 the PCR and the more sensitive PCR.

12          [Slide.]

13          In terms of time to response, Agouron found that  
14 about eight weeks was necessary for most subjects to reach  
15 1,200 copies. For Boehringer, eight weeks was also a  
16 reasonable time to reach 400 copies, although they found  
17 that 16 weeks was necessary for most subjects to reach 20  
18 copies.

19          [Slide.]

20          Glaxo found that about 12 weeks captured most of  
21 the responders.

22          [Slide.]

23          Merck found that 12 weeks to 16 weeks captured  
24 most of the responders using the PCR assay, although using

1 the more sensitive PCR assay, 20 to 28 weeks were necessary  
2 for all subjects to respond.

3 [Slide.]

4 So there are several interesting findings in these  
5 analyses. First, some subjects took longer than 20 weeks to  
6 reach the assay limit, and this seemed to depend primarily  
7 on the assay used and its lower value. For example, 1,200,  
8 most subjects were responding in six to eight weeks, but  
9 using the most sensitive PCR assay, subjects were responding  
10 16 to 20 weeks and beyond.

11 [Slide.]

12 So to find out more about those subjects who took  
13 the longest to respond, we asked the companies to provide  
14 individual patient RNA plots, and there is a couple  
15 interesting findings here.

16 First, is that not all of these subjects started  
17 at the very highest levels. Some started down 4 to 4.5  
18 logs, and in general, there was a downward trend, although  
19 there are definitely bumps along the way.

20 [Slide.]

21 Boehringer found a very similar thing. First,  
22 that the ones who took longer than 16 weeks didn't all start  
23 at the very high levels, some were even down below 10,000.  
24 There was a general trend downward, but there were still

1 fluctuations in achieving the lower limit.

2 [Slide.]

3 Overall, some conclusions would be subjects who  
4 take the longest to reach the limit, generally show gradual  
5 progress, although the RNA may fluctuate. This implies that  
6 subjects should not be classified as early failures if their  
7 RNA is detectable, but not increasing.

8 [Slide.]

9 The presentations also addressed the issue of  
10 baseline factors on the time to response. Here, stratified  
11 by baseline RNA, found relatively small differences on the  
12 order of two to four weeks in time to response.

13 [Slide.]

14 A similar pattern was seen for CD4.

15 [Slide.]

16 When Boehringer stratified by baseline CD4, again,  
17 about a four-week difference was seen.

18 [Slide.]

19 As well as for baseline RNA.

20 [Slide.]

21 Here, in Glaxo's analysis, the time to reaching  
22 the lower limit was again stratified by RNA, and you see  
23 while the proportion of subjects who eventually reach this  
24 400 copy lower limit is quite different between the

1 baselines, the actual time is not too different, here, on  
2 the order of perhaps six weeks.

3 [Slide.]

4 They found even smaller differences in the timing  
5 for the more experienced subjects, while again the percent  
6 responders was quite different.

7 [Slide.]

8 Merck found slightly larger differences, here,  
9 perhaps on the order of eight weeks, when stratified by  
10 baseline RNA in comparing the time to response, but did not  
11 find a CD4 difference.

12 [Slide.]

13 Overall, it seems that there was two distinct  
14 points, one, that the probability of eventually achieving  
15 the limit was quite different depending on baseline factors,  
16 such as CD4, prior treatment, and baseline RNA, but the time  
17 to response was, in general, more similar, sort of on the  
18 order of four weeks of difference.

19 [Slide.]

20 Next, we will turn to the second phase of RNA in  
21 these trials, the phase that gets at the durability of the  
22 responses..

23 [Slide.]

24 Here, Agouron showed that out close to a year,

1 there was still about an 80 percent response, and recall  
2 that this time here starts once subjects became responders,  
3 so that there is some time previous to this.

4           This also makes the point that the initial dose  
5 comparison, when looking at the initial rate of loss of  
6 response, was not really significant until you get out  
7 around 24 weeks after the first achieved response, and this  
8 has implications for future trial designs when you are  
9 looking at two effective treatments and you are trying to  
10 make more subtle distinctions.

11           [Slide.]

12           Overall, Boehringer found about a year was the  
13 median time to loss of response.

14           [Slide.]

15           Glaxo was only studying a two-drug combination, so  
16 that the loss of response occurred much earlier on, on the  
17 order of 16 weeks.   [Slide.]

18           Overall, to compare these two, you can see that  
19 while the two nucleoside combination had 50 percent of  
20 subjects fail by 12 to 20 weeks, the triple drug  
21 combinations generally lasted past 48 weeks, and in  
22 particular, the two nucleoside and one protease combination  
23 at 40 to 48 weeks still had about an 80 percent response.

24           This implies that if one wants to characterize the

1 durability of a particular regimen, and to characterize the  
2 durability at least, say, 50 percent of subjects will have  
3 failed, then, a 48-week study may not be short enough to  
4 characterize the durability of the more effective treatment  
5 regimens.

6 [Slide.]

7 The presentations also addressed the issue of  
8 baseline on the durability. Here, Agouron presented results  
9 that said when stratifying by RNA, there was a difference in  
10 durability.

11 [Slide.]

12 They identified smaller differences when  
13 stratifying by CD4, and they also noted that when they  
14 restricted their analysis to just the approved combination,  
15 the 750 mg, this difference went away.

16 [Slide.]

17 Boehringer found RNA to be very important, as  
18 well, in predicting overall durability, while baseline CD4  
19 they found was not an important factor.

20 [Slide.]

21 Glaxo, as well, found that for both the  
22 experienced and naive subjects, baseline RNA strongly  
23 influenced the eventual durability of the response.

24 [Slide.]

1           However, they, as well, found baseline CD4 was not  
2 an important predictor, although prior treatment was.

3           [Slide.]

4           Overall, RNA was important as a baseline predictor  
5 in determining overall durability of these treatments, and  
6 was more influential than CD4. This implies that the trial  
7 length will be strongly affected by the population studied.  
8 Less advanced populations may need much longer trials to  
9 determine when subjects are losing their durability. In  
10 contrast, more advanced subjects can get away with shorter  
11 trials.

12          [Slide.]

13          One additional question we were interested in was  
14 how the initial drop predicted the eventual durability.  
15 Here, Glaxo found for the naive subjects achieving 400  
16 resulted in a more durable response than not achieving 400.

17          [Slide.]

18          Although they did not find a difference in the  
19 more experienced subjects.

20          The next two slides are sort of the most  
21 interesting of all of the results presented.

22          [Slide.]

23          This slide found that the durability at 50 copies  
24 was longer than the durability between 50 and 500, which in

1 turn was longer than the durability of subjects who never  
2 reached 500. So this says that the more sensitive assays  
3 are really identifying a true response and that this  
4 response may result in much longer durabilities, which may  
5 also mean much longer trials.

6 [Slide.]

7 Here, there is another dramatic difference  
8 identified by the Boehringer analysis, that responses down  
9 to 20 copies were seen to be much more durable than  
10 responses which did not achieve 20 copies.

11 [Slide.]

12 Here again the median for this is out past a year.

13 [Slide.]

14 In making overall conclusions, it seems that the  
15 effect of maximal suppression is, in a sense, exponential,  
16 that not only do you get the benefit of a lower RNA  
17 response, but that response lasts for a longer time, and  
18 that is sort of consistent with what little is known about  
19 the resistance patterns in these studies.

20 One thing this implies is that the goal of therapy  
21 should be the lowest possible RNA level, in particular using  
22 the most sensitive assay, the lowest value, although again  
23 for advanced patients, this may not be a reasonable  
24 requirement and other requirements may be necessary.

1 [Slide.]

2 Now, I will focus on the last part of the RNA  
3 response, what happens after the RNA loses the initial  
4 suppression and begins to head back towards baseline.

5 [Slide.]

6 Agouron found that there were several small blips  
7 in the overall RNA curves and that judging someone to have  
8 lost their response after one value above the limit of  
9 quantification was not a good idea.

10 [Slide.]

11 Boehringer found, as well, that some patients do  
12 return to undetectable after rising above it.

13 [Slide.]

14 Overall, it seems that as a minimum, a  
15 confirmation of values above the detectable range would be  
16 necessary to avoid switching subjects off of effective  
17 therapy, and this definition of loss of response is still an  
18 open question. Perhaps 5,000 copies or some other number  
19 would be more appropriate in determining what a loss of  
20 response is, and this may be an individual patient decision  
21 depending on their particular CD4 count and whether it is  
22 worse to switch off an effective therapy too soon or stay on  
23 an ineffective therapy too long.

24 [Slide.]

1 Overall conclusions. The response was determined  
2 in these studies as achieving the assay limit, although  
3 again in advanced populations, this may not be achievable.  
4 The time to response may be as long as 16 to 24 weeks, so  
5 that subjects should not be switched off therapy on the  
6 basis of short-term fluctuations.

7 When defining a loss of response, a flexible  
8 definition would be necessary, especially to avoid the  
9 problem that Agouron found, that their CD4-based definition  
10 would have resulted in many subjects being switched off  
11 effective therapy.

12 Finally, the time to loss of response may be 48  
13 weeks or more after achieving that response, especially as  
14 treatment regimens get better.

15 Thanks.

16 DR. HAMMER: Thank you.

17 Are there questions for Dr. Elashoff? Jim.

18 DR. LIPSKY: At the beginning of your talk, you  
19 referred to the reappearance of viral RNA as inevitable. Do  
20 you have evidence that that is correct, and curiosity would  
21 be with the highly active protease inhibitors and to  
22 nucleoside inhibitors, do you have that data?

23 DR. ELASHOFF: I didn't mean that literally.

24 DR. HAMMER: Other questions? John.

1 DR. MODLIN: Even though the time to loss of  
2 response obviously may extend beyond a year, beyond 48  
3 weeks, as several of the data sets have shown, it looks like  
4 to me that whenever two or more regimens are being compared,  
5 that most of the differences between those regimens occur  
6 within the first six months, and this seems to me to have  
7 recurred in study after study that has been presented, and  
8 you have shown the same data today.

9 I really bring that up as more of a comment. Do  
10 you see the same thing in the data that I do?

11 DR. ELASHOFF: Yes, I see the same thing. If you  
12 are only interested in detected differences, those can  
13 certainly be less than 48 weeks. If you are interested in  
14 knowing how durable the response would be and say putting in  
15 the label what is the median durability, then, you need to  
16 follow for much longer.

17 DR. HAMMER: Although that may change as clinical  
18 trial design changes where potent regimens are put up  
19 against each other, and it may not be so apparent in the  
20 first 16 to 24 weeks.

21 Mark, did you have a comment?

22 MR. HARRINGTON: No, you just said what I was  
23 going to say.

24 DR. HAMMER: Thank you very much.

1 We are going to move on the open public hearing.

2 **Open Public Hearing**

3 DR. HAMMER: I am going to announce individuals in  
4 order. I would ask them to please keep their comments to  
5 five minutes or less, and please make any financial  
6 disclosures that are relevant, and if there are no  
7 disclosures to make, please so state.

8 The first individual signed up is Ben Cheng from  
9 Project Inform.

10 MR. CHENG: Good morning. My name is Ben Cheng.  
11 I am with Project Inform in San Francisco. Project Inform,  
12 the vast majority of our budget comes from personal  
13 donations, however, we do receive pharmaceutical funding  
14 from a number of pharmaceutical companies.

15 I think that there is overwhelming evidence that  
16 sustained reduction in viral load correlates with clinical  
17 benefit in the vast majority of the studies that have been  
18 presented. However, I think the sort of more difficult  
19 question now is how do we design clinical studies with new  
20 antiretroviral drugs in the age of protease inhibitors, and  
21 I think that there is an urgent need in having a forum or a  
22 meeting or something that discusses that issue.

23 We would agree with Mark Harrington that AZT/3TC  
24 should not be considered an adequate control arm and there

1 needs to be some discussion as to what would constitute an  
2 adequate control arm these days.

3           Project Inform has also been a long advocate of  
4 strategy studies based on real-time viral load monitoring,  
5 as well as I think these days with genotyping and  
6 phenotyping resistance as these tests are commercially  
7 available and patients are using them to guide their  
8 treatment regimens, although I think that there is very  
9 little understanding as to what some of these results might  
10 mean.

11           There also needs to be a mechanism to look at  
12 long-term followup. I think with some of the postmarketing  
13 studies, there hasn't been adequate long-term followup as we  
14 are now seeing some sort of strange side effects coming from  
15 some of the protease inhibitors that were not seen in the  
16 clinical studies.

17           Additionally, I think that there needs to be some  
18 population-based pharmacokinetic studies to look at drug  
19 levels in people with wasting disease and between men and  
20 women, and early versus late disease also as there are  
21 significant differences in some of these people that we have  
22 heard through our hot line.

23           Thank you very much.

24           DR. HAMMER: Thank you.

1           The next speaker is Ron Baker, Director of  
2 Treatment Education and Advocacy and Editor and Chief of  
3 Beta.

4           [No response.]

5           DR. HAMMER: He spoke yesterday. Is he making any  
6 comments today? No?

7           The next speaker then is Jules Levin from the  
8 National AIDS Treatment Advocacy Project.

9           MR. LEVIN: Hi. My names is Jules Levin. I am  
10 from New York with the National AIDS Treatment Advocacy  
11 Project. I am also a person with HIV.

12           Even though there is no product that is the  
13 subject of this hearing, I will disclose my financial  
14 information. We receive support from a number of  
15 pharmaceutical companies, as well as from private and  
16 corporate sources.

17           I think the subject of the hearing in general  
18 here, I don't really need to comment on. I agree with what  
19 Ben just said, that the data seems overwhelmingly convincing  
20 that viral load changes due to treatment effect do correlate  
21 with clinical progression and disease progression.

22           So, I support a change, and I have supported a  
23 change for about a year now, even before. Now the FDA says  
24 RNA is validated, even before the FDA admitted that RNA was

1 validated, I supported it then. I think we do need to make  
2 this change because it is probably no longer feasible or  
3 ethical to conduct traditional clinical endpoint studies.

4 So I just want to make a few points. I do  
5 strongly support, and will continue to support vehemently,  
6 accelerated approval. And I would like to talk briefly  
7 about double nucleoside therapy as a comparison arm.

8 I think we are getting mixed messages about using  
9 double nucleoside therapy. For example, it is being used in  
10 comparison arms and in studies, and the FDA is permitting it  
11 to be used, and the FDA has said that they have no control  
12 over that, and nonetheless, the PHS guidelines and the  
13 industry itself, as well as most of the researchers, are  
14 recommending the goal of therapy should be full suppression  
15 to 400, 200, probably even 20, and obviously, that is  
16 probably unreachable and not sustainable with double  
17 nucleoside therapy. So what are the ethics of using double  
18 nucleoside therapy in a clinical trial?

19 And so why should the FDA persist with this  
20 requirement of proving superiority, because I think that is  
21 one of the factors in why double nucleoside therapy  
22 continues to be used as a comparison arm.

23 If the FDA might drop this need for proving  
24 superiority, maybe we could--I think I agree with what Ben

1 said, there probably needs to be a much broader, longer  
2 discussion about how to handle this situation, as well as I  
3 think maybe he was just talking about how to design clinical  
4 trials, but I think we do need a broader discussion of this  
5 to address this, as well as a broader discussion to discuss  
6 how to address new clinical trials.

7           Treatment strategy trials have been suggested as a  
8 model, and I think that we have seen over the course of the  
9 last year or so the challenges that really face us in trying  
10 to adapt what we need to do here inside of a format of  
11 treatment strategy trials, and that probably needs to be  
12 broadly addressed, because I personally can't stand here  
13 today and tell you what I think we should do.

14           I think that there are a lot of challenges we face  
15 in designing new clinical trials, treatment strategy trials,  
16 as well as formatting all of this information into clinical  
17 trials, but that is what the industry and the FDA get paid  
18 for, to design these trials, so I think that is the  
19 responsibility of academia, the industry, the FDA, and I  
20 know for myself and other people in the community, we will  
21 be glad to participate in trying to help evolve this issue.

22           One important fact I want to mention is what  
23 William Cavert discussed yesterday, was also brought up down  
24 in Florida with regards to double nucleoside therapy and any

1 therapy that doesn't suppress adequately.

2 I think it was said in Florida at the resistance  
3 meeting that partial suppression with regards to suppression  
4 of viral load in lymph tissue probably does more harm than  
5 no suppression at all.

6 So if we are trying to suppress in lymph tissue--  
7 which we are--I think that is another point to consider in  
8 the need for full suppressive therapy. That was another  
9 issue that I think we need to discuss, too, what is full  
10 suppressive therapy. It probably doesn't seem like one  
11 potent protease inhibitor plus two nucleosides is any longer  
12 the standard of care in my progressive point of view,  
13 especially in a more advanced population.

14 So I would like to hear the panel address that  
15 issue. I think we are moving towards the need for much more  
16 suppressive therapies in an advanced population, as well as  
17 I would like to hear the panel discuss the issue of double  
18 nucleoside therapy with regards to clinical trials and  
19 therapy in general and with regards to the FDA.

20 I would like to hear an FDA comment on that also  
21 considering that, you know, at the May 16th meeting they had  
22 with us, they told us that it is not within their purview or  
23 mandate to rule on double nucleoside therapy use, that it  
24 should be left to the IRBs, and I do think that as more

1 information goes out from the PHS guidelines, and so forth,  
2 that IRBs will have more knowledge and capacity to rule on  
3 studies that have double nucleoside therapies, and they may  
4 reject the studies when they get that far, but I don't feel  
5 comfortable with trusting IRBs in certain parts of the  
6 country even in, you know, big cities with that kind of  
7 decision. I am not sure that they are well educated and  
8 informed enough to do that.

9 I just finally would like to take this opportunity  
10 to remind everybody that a very important issue is  
11 individuals who have failed protease therapy and what are we  
12 going to do at this point, and I know that--and I think we  
13 all should take some responsibility for this failure.

14 The drugs were not used properly in many instances  
15 and we are now learning that one protease and two NUKS may  
16 not have been appropriate therapy at all for some  
17 individuals, so I think that everybody bears some  
18 responsibility for this including the community.

19 But what are we going to do now? And I think that  
20 we need to address this issue, a very, very pressing issue.  
21 Many people can't wait too long for new drugs, many people  
22 can wait for new drugs, but how are we going to address  
23 this?

24 I know that there are ACTG and industry studies

1 that will be addressing this issue, but I am not convinced  
2 that we are addressing this adequately, and it is a very  
3 concerning issue for people in the community, and I think  
4 that we should try and do more and try to do as much as we  
5 can to address this issue as quickly as we can.

6 Thank you.

7 DR. HAMMER: Thank you.

8 The next speaker is Spencer Cox from the Treatment  
9 Action Group.

10 MR. LEVIN: One last thing I just want to say that  
11 I do strongly support the need to do follow-up studies and I  
12 think at the American Abbott hearings last year, the  
13 companies did commit to this, and companies seemingly do  
14 want to commit to doing strong follow-up studies, but it is  
15 very important that we actually insist upon long-term  
16 followup for safety and efficacy, what are these drugs going  
17 to do in three, five, 10 years.

18 DR. HAMMER: Thank you.

19 MR. COX: Hi. The Treatment Action Group receives  
20 most of our funding also from private donors and  
21 foundations, however, I think it is about 15 percent of our  
22 income comes from pharmaceutical companies including the  
23 manufacturers of most of the major marketed and experimental  
24 anti-HIV drugs. I unfortunately don't have the list right

1 in front of me.

2 I think there are a number of issues and I guess  
3 in some ways I am agreeing with Ben and Jules. There are a  
4 number of issues that face us here today to which the  
5 presentations that have been made are in some ways only  
6 partially responsive.

7 We are facing a situation in which it is clear  
8 that clinical trials are going to have to change in order to  
9 accommodate the medical needs of the patients who are  
10 enrolled in those trials.

11 I certainly support such a move and think that we  
12 need to do so as fast as possible, but I also think it is  
13 important to remember that these trials are fulfilling  
14 another set of needs, a set of regulatory needs in  
15 evaluating the specific claims that are made about the  
16 safety and efficacy of products, and it is important not to  
17 lose sight of those claims as we move towards larger  
18 strategy trials, because that function that these studies  
19 are meeting will ultimately lay the groundwork for future  
20 therapeutic improvements.

21 One of the things I am sorry we didn't see during  
22 these presentations is any sort of discussion of past  
23 failures of surrogate markers. We have certainly seen them  
24 in the past, markers that in general perform well, every now

1 and again we will have a great big stumper resulting in  
2 premature deaths for a lot of people, and I do think it is  
3 important to recognize that and to try and think, as we are  
4 moving towards an RNA-based standard, how we are going to  
5 try and avoid making some of the mistakes that have been  
6 made in the past.

7 I also think it is important, like Ben, to have a  
8 discussion of trial design issues. Obviously, the FDA's  
9 interpretation of their regulations will impact the way that  
10 both academic and industry studies are designed.

11 In particular, it seems to me that there are  
12 questions about the choice of the measure of RNA response  
13 and the choice of control arms, as has already been  
14 discussed, that are exceedingly vexatious at least to me,  
15 and maybe that is just because I am dense, but there is some  
16 discussion that could still occur.

17 It also seems to me that if we are going to make  
18 this change, we need to think very carefully about how we  
19 monitor the safety of these therapies. We are still  
20 discovering in the post-approval setting, serious, adverse  
21 events associated with these products.

22 There are rumors floating everywhere about even  
23 new ones that haven't been described yet, and as we are  
24 sacrificing the ability to make the long-term clinical

1 judgment, the use of a therapy is more helpful than not  
2 using the therapy, then, we need to think very carefully  
3 about how we look for adverse events.

4           It also seems to me we should be thinking about  
5 what kinds of supportive data would be needed for an  
6 entirely RNA-based application. There was a drug, for  
7 example, recently approved for which serious interactions  
8 had been identified with therapies that were likely to be  
9 used in combination. I am speaking obviously of  
10 delavirdine, but for which there was really no safety or  
11 activity data.

12           That really scares me very much. I certainly know  
13 people who are using combinations of protease inhibitors and  
14 delavirdine. I am hearing anecdotes of adverse events, but,  
15 you know, there is nothing systematic to look at to judge  
16 this is even, in fact, safe.

17           Then, finally, I think it is important that the  
18 committee not offer FDA carte blanche, just say, well, in  
19 general, we think RNA is a good thing, so go for it. I  
20 think the committee should put some time and energy into  
21 really thinking about how this change needs to be made and  
22 what its impact is going to be on clinical care, because the  
23 impact is going to be enormous one way or the other, we are  
24 going to make some tradeoffs, and I hope those tradeoffs

1 will be made after some public discussion about what the  
2 risks and benefits of various factors are.

3 Thank you very much.

4 DR. HAMMER: Thank you.

5 The next speaker is Linda Dee from AIDS Action  
6 Baltimore.

7 [No response.]

8 DR. HAMMER: Iris Long from AIDS Coalition to  
9 Unleash Power.

10 [No response.]

11 DR. HAMMER: Linda Grinberg from the Foundation  
12 for AIDS and Immune Research.

13 [No response.]

14 DR. HAMMER: Bill Bahlman from ACT UP - New York.

15 MR. BAHLMAN: Good afternoon or good morning. We  
16 are doing well on time. Hopefully, we can catch earlier  
17 trains and planes back home and move quickly on these  
18 decisions. There is a lot still to be discussed.

19 I am with ACT UP - New York. I am a founding  
20 member of the organization. My organization does not accept  
21 pharmaceutical company grants, but I have accepted a number  
22 of scholarships to attend scientific forums around the  
23 world, only a few of them, but I wanted to make that known,  
24 although I feel absolutely no--that has not presented the

1 least bit of conflict of interest with all the friends I  
2 have lost to AIDS and the fact I have been battling HIV for  
3 10 years myself.

4 I want to thank the FDA for finally holding this  
5 forum. I think it's long overdue. I also would like to  
6 thank the FDA for the way in which it approved the protease  
7 inhibitors that came before the FDA and this committee.

8 I think Jeff Murray did a brilliant job in  
9 analyzing the data and putting forth a scenario and a basis  
10 for understanding how to use these drugs based on the data  
11 that was brought forth by the sponsors, and I want to thank  
12 Jeff. I think he has done a very wonderful job.

13 I have guarded optimism today. Many of us in the  
14 community have fought for the last year and a half for a  
15 hearing such as this and to accept viral load and to  
16 eliminate clinical endpoint studies, which, you know,  
17 clinical endpoint studies sound as if, you know, we are just  
18 counting endpoints, you know, we are counting people getting  
19 very sick, we are counting people dying.

20 This has not been necessary for quite some time  
21 now. When Merck's Crixivan/indinavir came before this  
22 committee, a number of us--and I was picked as a point  
23 spokesperson for quite a few organizations--to speak out  
24 against ACTG 320, to say that this study should not move

1 forward, it is unethical at this point based on what we were  
2 seeing from surrogate marker studies, viral load studies,  
3 that showed that AZT/3TC could not give anywhere near the  
4 response, could not bring people to undetectable levels and  
5 keep them there, as the AZT/3TC/indinavir arms clearly did.  
6 There was no question about that.

7           The representative from Project Inform to Jules  
8 Levin to myself, to many other people who were here, Linda  
9 Grinberg, and yet that study moved forward. I have guarded  
10 optimism because the chair of this committee was the  
11 protocol chair of 320, but I am glad that study is stopped  
12 and less deaths occurred and less illnesses occurred than  
13 might have if the study had continued to move forward.

14           I am glad it stopped, but a lot was said in  
15 support of that study, that to me did not really bear  
16 scientific credibility. There were a lot of excuses made  
17 for continuing of that study, and I am glad it is finally  
18 stopped. I couldn't agree with any of those excuses.

19           I am also concerned because of the many people who  
20 have been very outspoken for accepting viral load as a true  
21 marker of progression, not one of the very outspoken people  
22 over a long period of time was asked to be a patient  
23 representative of the committee, but, you know, we do have  
24 two patient representatives, and I think we should also be

1 cautious in terms of plans to have permanent representatives  
2 or patient representatives being on this committee, but I  
3 must also agree with Mark Harrington in his comments about  
4 the Glaxo 3TC/AZT control arms. We must do away with those.

5 I must also mention that it took quite some time  
6 for a number of conservative people in the research  
7 community and doctors to accept combination therapy as the  
8 way to move forward.

9 We must look at history as we look to the future,  
10 and a lot of the changes that need to be made have been  
11 first recognized by the progressive members of the community  
12 and most of all us in the community before they have become  
13 the rule of the way we do things, and the time lag from when  
14 we realize those things to when we implement them continues  
15 to be so long, far too long, and irresponsibly long if you  
16 ask me.

17 We have seen great progress in the last two years.  
18 New reports were in the press yesterday about the extension  
19 of lives and fewer people dying. I think the new reports  
20 referred to now over the first nine months of 1996 we are  
21 seeing fewer deaths as opposed to the initial six months  
22 that was first reported.

23 Of course, this is due to combination therapy, and  
24 it is due to the use of protease inhibitors. This period is

1 increasingly being referred to as a honeymoon period. Now,  
2 what is a honeymoon period? A honeymoon period is something  
3 that ends unless we keep the honeymoon going.

4 I fear we may not do that. The way the drug  
5 companies have been slow, some slower than others to get  
6 expanded access programs going is atrocious, it is  
7 irresponsible.

8 I was attending a forum on feedback symposium on  
9 the St. Petersburg conference, and one of the things I think  
10 we are learning, the more progressive, the more outspoken  
11 researchers in our community, and our community people is  
12 that for treatment failures, you know, we need to maybe hit  
13 the virus even harder for these patients than we do with  
14 initial therapy.

15 That means maybe three new drugs. Will the drug  
16 companies cooperate with their expanded access programs, at  
17 the very least, have their CROs that are administering the  
18 programs for them refer patients to other expanded access  
19 programs, so that there can be more of a collaborative and a  
20 cooperative access to new drugs? Also, will we take what we  
21 learned here today and make sure that people gain access  
22 through accelerated approval quicker and understand that  
23 that need is still great?

24 I think I pretty much covered a lot of things that

1 I had here. I have about four of five sheets of paper, and  
2 the notes were everywhere, but I was probably a little bit  
3 more succinct than I thought I would be.

4 But I just think it is very important and I don't  
5 want to see control arms that are substandard ever again. I  
6 don't want to see the FDA allow it. I don't want this  
7 committee to accept it. I look forward to seeing progress  
8 made on that level, so I thank you very much and have a good  
9 day, and let's move forward quickly.

10 DR. HAMMER: Thank you.

11 Is Emmanuel Trenado here?

12 [No response.]

13 DR. HAMMER: The next speaker is John James from  
14 AIDS Treatment News.

15 MR. JAMES: Hello. I am John James, editor and  
16 publisher of AIDS Treatment News. A number of  
17 pharmaceutical companies subscribe to our newsletter, but by  
18 far, most of our income is from individuals not affiliated  
19 with the companies.

20 I want to emphasize some points already made by  
21 others. First, it is clearly wrong and unworkable to keep  
22 people on treatments in trials that are not working for  
23 them, and also we desperately need more antiretrovirals  
24 because the ones we do have do not work for many people.

1           The FDA has a critical role in establishing a  
2 clear and workable path for companies to bring these new  
3 drugs forward.

4           HIV viral load has now become established as  
5 important in medical practice by a very wide consensus of  
6 physicians and scientists. It is not and never will be the  
7 only information doctors need and use.

8           The FDA should accept this professional consensus  
9 and label drugs for reducing viral load, not second-guess  
10 the ultimate importance of viral load for every new drug or  
11 even for every new class of drugs.

12           There is growing agreement that companies must  
13 give physicians a workable package of information for using  
14 their drug. That means we need more of the small, rapid,  
15 easy and safe PK testing to develop doses and formulations  
16 for children, to look for gender differences, and to examine  
17 more of the clinically important potential drug  
18 interactions.

19           The FDA should require that companies determine a  
20 dose for children or explain why not at least before  
21 confirmatory approval.

22           The success of viral load must not lead to further  
23 neglect of other kinds of therapies. Yesterday, David  
24 Scondras asked the FDA to assemble a roundtable to get

1 faster movement on immune markers.

2           There are potential candidate markers which are  
3 well known today, and their development has been seriously  
4 delayed by lack of attention and support.

5           The committee and the FDA should be commended for  
6 this excellent effort which focuses on the most central  
7 issues and examines the evidence in depth.

8           DR. HAMMER: Thank you.

9           The next speaker is Mike Donnelly from ACT UP -  
10 Golden Gate.

11           MR. DONNELLY: I am Mike Donnelly from ACT UP -  
12 Golden Gate. We accept no pharmaceutical money. I have not  
13 personally accepted any money either.

14           ACT UP - Golden Gate believes that HIV RNA  
15 suppression does show evidence of clinical benefit and hopes  
16 the committee recommends its use for approval of new  
17 antiviral drugs. Too many PWAs need new therapy choices.  
18 Approval of new drug appears to be the only way to access  
19 new drugs especially for drug-experienced PWAs.

20           A few years ago I had zero CD4s, a viral load of  
21 146,000, and starting to get KS. I lost the protease  
22 lotteries held by the drug companies which will never happen  
23 again. Lotteries for our lives are unacceptable.

24           I stopped antiviral therapy because I had no new

1 choices until the protease inhibitors were approved, and I  
2 have responded. I now have 300 CD4s, about the number I had  
3 nine years ago when I had my first CD4 count.

4 I have an undetectable viral load and no KS, and  
5 most important, I feel better. We need new choices.

6 This year, two of our ACT UP - Golden Gate  
7 members, Dean Knudsen and David Milstein, died while waiting  
8 for a 1592. We need new choices.

9 Shame on Glaxo for their woefully inadequate  
10 expanded access program for 1592. We need new choices.

11 While it is important to keep gathering data for  
12 new therapy for long-term use, we need access as soon as  
13 possible. We have heard evidence these last two days  
14 showing HIV RNA viral suppression as an adequate endpoint  
15 for approval of antiviral drugs. We hope the committee  
16 recommends the use of them.

17 Approval equals access, access equals life.

18 DR. HAMMER: Thank you.

19 The next speaker is Beverly Dale from Roche  
20 Molecular Systems.

21 DR. DALE: I am Beverly Dale and I am employed by  
22 Roche Molecular Systems, which is the manufacturer of the  
23 Amplicor Monitor PCR-based viral load assay that has been  
24 referred to often today, and I wanted to make a comment to

1 the committee about the issues of differences in the level  
2 of quantitation versus the level of detection, and then  
3 comment on how that might reflect on how testing  
4 laboratories report back to their pharmaceutical customers.

5           What I am saying applies to PCR technology, but I  
6 believe it probably applies to any of the other technologies  
7 that are being used or considered.

8           First of all, in our FDA-approved kit, the limit  
9 of detection is stated in the package insert as less than  
10 400 copies/mL. What that means is that the FDA has approved  
11 linearity to 400 copies/mL, but in fact, when you do the  
12 assay, because of the way it is constructed, you may get  
13 something like 100, 200, 300. Those are real viral titers,  
14 but they are not linear, if you will, and a true negative is  
15 truly below whatever the detection limit, if you will, of  
16 the assay is.

17           The preparation that we are making for the 50 copy  
18 assay will have the same issues associated with it, and that  
19 is, you can come up with a number above 50, which is  
20 quantifiable, but you may also come up with numbers like 10,  
21 20, 30, which are detectable, but not considered linear or  
22 quantifiable.

23           So what I am suggesting is for the purpose of  
24 clinical trials, there are really three interesting patient

1 groups here. One would be--let's use 50 copy assay as an  
2 example--patients that are quantifiable above 50, patients  
3 that are not quantifiable, but actually do give a true  
4 virologic number or titer, if you will, and the negative  
5 patients, and perhaps in that third group, in the middle,  
6 when we look at the type of data evaluations that have been  
7 presented, there will be interesting things coming out.

8 DR. HAMMER: Thank you very much for that  
9 qualification.

10 Those are all the individuals that are signed up  
11 officially for the public hearing. Is there anyone else who  
12 wishes to make a public statement?

13 [No response.]

14 DR. HAMMER: If not, we will break for lunch and  
15 be back at 12:20. Thank you.

16 [Whereupon, at 11:20 a.m., the proceedings were  
17 recessed, to be resumed at 12:20 p.m., this same day.]

1 AFTERNOON SESSION

2 [12:35 p.m.]

3 DR. HAMMER: The first point on the agenda for  
4 this afternoon's session is the charge to the committee by  
5 David Feigal.

6 **Charge to the Committee**

7 DR. FEIGAL: I would like to begin by thanking  
8 everybody, both in the Division and the companies who I  
9 think collaborated in a very helpful way to give us some  
10 actual data to look at for some of the proposals that have  
11 been made and considered for some period of time.

12 This committee has been asked in the past several  
13 times to consider how to design trials for HIV disease. In  
14 the earliest time period, we wondered about how to detect  
15 active diseases, what types of surrogate markers would  
16 reliably predict a drug that would have a clinical benefit.

17 There was a time when we felt that we may be in an  
18 era where we had drugs with such modest effects that it  
19 would require large trials, and the sense of this committee  
20 even a couple of years ago was that the typical clinical  
21 trial of 1,000 patients was probably underpowered and that  
22 we needed 3- to 5,000 patients to detect the kinds of  
23 clinical benefits that we would see with HIV disease.

24 There has been an increasing call for strategy

1 trials and there have been some examples of such trials  
2 trying to look at early therapy, early monotherapy versus  
3 early combination therapy, strategies such as maximal  
4 suppression versus regimens which are less than maximal  
5 suppression, but may spare drugs and leave therapeutic  
6 options, but as yet those have not yet materialized into  
7 things that have helped us in very many situations.

8           What we are looking at today is really sort of how  
9 are we going to use viral load, the CD4 counts in our trials  
10 in this next period of time, and it would probably be  
11 presumptuous for us to assume things have settled down that  
12 we can predict more than a couple of years at a time in this  
13 business, but I think we could actually start by phrasing  
14 the question in the reciprocal, which is what are our  
15 alternatives to using viral load and CD4 count.

16           If we did not use them in some ways to help us  
17 stratify trials, detect response to drugs, pick doses, we  
18 would largely be stuck using fixed regimens until we  
19 developed dose-limiting toxicity or observed clinical  
20 progression or some other evidence of benefit or lack of  
21 benefit.

22           The other question that has often been asked in  
23 this area is, well, what is the usual paradigm for treating  
24 infectious disease, and is viral load really a surrogate

1 marker or is it, in fact, a measure of HIV disease.

2           We have two goals. We have the goal of preventing  
3 the complications of the acquired immune deficiency  
4 syndrome, which is all of the problems created by the immune  
5 deficits, but the argument has been made that there are many  
6 infectious diseases that are successfully treated by  
7 following cultures, antigens, and other measures, direct  
8 measures of the disease, and I think we can be fairly asked  
9 are we torturing ourselves too much not to realize that that  
10 may be the situation we are with some of our measures of HIV  
11 virus.

12           When we look at the paradigms for treating  
13 bacterial infection diseases, I think there are some  
14 interesting parallels. Some bacterial infections are  
15 treated empirically. Children with otitis media, you  
16 usually don't get after a culture. It requires broad  
17 spectrum, perhaps sometimes broader spectrum than if you had  
18 the specific organism, and you assess the efficacy of those  
19 treatment paradigms by clinical failures and then sometimes  
20 by follow-up cultures of your clinical failures.

21           But most of the treatment of infectious diseases  
22 is based on individualizing therapy, individualizing it  
23 based on different ways of assessing whether the organism  
24 will respond.

1           With bacteria, that is often done with sensitivity  
2 measures, and in fact, if you look at the labeling for most  
3 antimicrobial products against bacteria, they are only  
4 approved for sensitive organisms. There is no expectation  
5 that you should treat someone who has pneumococcal pneumonia  
6 with a pneumococcus that is resistant to an antibiotic.

7           When you don't have sensitivity, how else do you  
8 look for the organism responses? The traditional measures  
9 of microbial response have been cultures turning sterile,  
10 drops in colony counts in the case of MAC bacteremia.  
11 Antigen falls are examples with both viral and fungal  
12 disease, and some drugs not suited for empiric treatment can  
13 be effectively used in individualized treatment.

14           There are antimicrobials which, at the time they  
15 are approved, 80 or 90 percent of the organisms are  
16 sensitive, and after 10 years of use, it may be 30 percent  
17 that are sensitive. The antimicrobial is still effective  
18 for the sensitive organisms, but it illustrates the  
19 importance of knowing what you are treating and whether or  
20 not the microbe is likely to respond.

21           I think much of what began by necessity with early  
22 HIV treatment was empiric therapy. We didn't have very many  
23 agents, we had no rational way to really adjust dose on an  
24 individual patient-by-patient basis, and it was largely an

1 era of empiric treatment, and I think one conclusion of the  
2 Division that I think should have come through in the last  
3 few days is that we don't think it is very satisfactory any  
4 longer to treat HIV empirically on fixed regimens, and not  
5 individualized patient and organism by specific ways.

6           So our basic tool in individualizing therapy HIV  
7 that we have looked at in this meeting is the basic tool of  
8 response. Looking for responders is a term which should  
9 make most clinical trialists and statisticians a little bit  
10 queasy, but there are appropriate ways, methodologically sound  
11 ways to use this tool.

12           Since baseline characteristics affect the  
13 response, and because some of the individual biologic  
14 variability of the assay is of larger magnitude than the  
15 effects of some of the weaker drugs, we still need to have  
16 control trials. We will usually not be able to figure out  
17 advances just by comparing people to their own baselines,  
18 and randomization can be kept intact by taking a look at  
19 time to loss of response, and the people who never have a  
20 response have a time to response of zero.

21           There are a number of challenges, and I think we  
22 have tried to illustrate some of those challenges on a  
23 databased way during this meeting. It should be quite  
24 obvious that the ability, the very way that we measure viral

1 load is a constantly moving target.

2           There is inherent biologic variability that is  
3 something that will not go away even as we approve the  
4 assays, and importantly, there are responses worth having  
5 because they are associated with survival benefits and  
6 progression benefits even when you can't achieve the optimal  
7 treatment and the ultimate goal.

8           Individualizing therapy requires that we able to  
9 have decision rules, however, and not just follow the  
10 markers. We need to be able to define cut points, we need  
11 to be able to have regimens for measuring endpoints, we need  
12 to have adequate followup, so that we are not getting biased  
13 estimates by virtue of people dropping out for nonrandom  
14 reasons.

15           So we have taken the questions about viral load,  
16 and we have phased them in different study phases that  
17 probably are best described by the yellow U-shape curve from  
18 Dr. Elashoff as he shaded in the different parts.

19           There is a part of the study phase which we would  
20 propose where it is appropriate to assess how well you have  
21 induced a response. You have a new agent or a new  
22 combination of agents, and how well are you able to get the  
23 organisms, get the virus, the swarm of virus that an  
24 individual patient has to respond during that time period.

1           That is a time period when most patient can stay  
2 on therapy and we can get a good estimate of the magnitude  
3 of the response, and we should do it across a spectrum of  
4 patients that have been pretreated with other agents and are  
5 naive to therapy, who have a high viral load, as well as low  
6 viral load.

7           Then, in the patients where there is a response  
8 that has been induced, we need to be able to monitor the  
9 duration of that response, and very importantly, when that  
10 response is lost, we need to evaluate what is the cause of  
11 that loss of response and what to do next.

12           Resistance is a problem, it is a very serious  
13 problem, but it is not the only reason for a loss of  
14 response, and all of the issues which have been mentioned at  
15 this meeting including drug interactions, poor absorption of  
16 the product, or other reasons for loss of response, or for  
17 things even unrelated to the drug therapy, a burst of viral  
18 replication from an intercurrent illness or a vaccination,  
19 we need to make sure that when we think we have seen a loss  
20 of response, that we are able to distinguish whether that  
21 means we have lost the agents that we are currently treating  
22 with.

23           There are certain gray zones, and I think many of  
24 the presenters have really addressed what some of those are.

1 There are patients who respond very slowly, and they are  
2 steadily responding, but if we had an arbitrary cutoff rule,  
3 they may be arbitrarily declared as failing those regimens.

4           There are patients whose setpoint is lowered and  
5 have a partial response. How do you know if that is all the  
6 best you can do, and how do you know which agents to stop  
7 and which agents to add? I think these are questions we  
8 haven't really answered yet.

9           As has been illustrated empirically from the data,  
10 there are many patients who transiently lose response and  
11 then without a change in therapy, appear to recover that  
12 response. What exactly is going on with all of that?

13           From a regulatory standpoint, what we are looking  
14 at is moving away from a label which simply says this agent  
15 is approved to treat HIV infection to a label that would  
16 describe the performance characteristics of the product.

17           There needs to be some sense to use these products  
18 clinically, to know how long to wait for a response, to have  
19 some sense of what the magnitude of response is, so you can  
20 individualize the therapy to baseline viral load levels.

21           You need to have some sense of how long you expect  
22 that response to last and what kinds of things need to be  
23 done to evaluate what to do when the response is lost.

24           A lot of the discussions and some of the public

1 comments really framed this a clinical endpoints versus  
2 viral load, and really this is not an either/or kind of a  
3 situation. There is no reason why these study designs can't  
4 be used with patients with clinically active disease, who  
5 have advanced disease, who are going to be developing  
6 clinical complications, and we can address and we will have  
7 a mechanism for looking for the agents that paradoxically  
8 make things worse or confer no benefit compared to a proven  
9 satisfactory regimen.

10 But there is still, I think, an ethical dilemma  
11 that has been raised by our ability to detect responses,  
12 which is that we--and this has been referred sometimes by  
13 the phrase "suboptimal regimens"--but I guess I would phrase  
14 it a little bit differently. I would say that we do not  
15 want to end up choosing up study designs that leave  
16 participants in worse shape than they would have been had  
17 they not participated in the study.

18 Now, part of the older rationale was to say, well,  
19 if the person is doing better than their baseline when they  
20 entered the study, then, they are probably better off than  
21 had they been in the study, and that was actually, if not  
22 explicitly, implicitly part of the evidence that was often  
23 presented for past approvals. You would see a CD4 count  
24 that had gone above baseline and that was above baseline at

1 six months, and it was above what at the time the trial  
2 started, was a good regimen.

3 But I think we are beginning to realize that it  
4 isn't that simple anymore, because better than baseline may  
5 exist, but you still may have burned some important  
6 therapeutic bridges.

7 Nonetheless, I think we need to make sure that we  
8 don't treat optimal as a simple question, because this is a  
9 disease that needs to be treated for a long period of time.  
10 What is optimal in the short term may not be optimal in the  
11 long term, and we need to be able to study the tradeoffs of  
12 saving agents with simpler regimens versus maximal therapy,  
13 and even though various advisory groups have taken stands in  
14 one direction and the other, in my mind at least, these are  
15 still open questions.

16 I think I would sort of summarize these last two  
17 days as saying that the details are complex, but the goal is  
18 simple. We want to create the incentives in drug  
19 development that we find agents that have the longest  
20 durable response as possible and that preserve the maximal  
21 therapeutic options.

22 Thanks very much.

23 DR. HAMMER: Thank you, David.

24 **Committee Discussion**

1 DR. HAMMER: We are now moving into the last  
2 session of the program, which will be the committee  
3 discussion. There are a number of specific questions that  
4 the Agency has posed to the committee, but before we get to  
5 those, I want to give the members of the committee an  
6 opportunity to comment essentially on the basic premise of  
7 these two days, as well as perhaps some of the data sets  
8 that we have seen in more general terms.

9 I will go around the table and ask you to please  
10 comment, if you have got questions about the issue of using  
11 RNA as an endpoint in trials with the new label indication,  
12 and to avoid getting into too much of the specifics around  
13 the discussion points that we will then take in sequence.

14 If you have no comments and wish to defer to the  
15 questions, that is fine. If you have got general comments  
16 now, please give them to us.

17 I will start with Mark.

18 MR. HARRINGTON: Right. Thanks.

19 I think we are going to address the discussion  
20 points as written, but I want to address sort of what is  
21 missing because I think this discussion can't take place in  
22 a vacuum.

23 I think there is general consensus that we need to  
24 move to an RNA-based approval standard, but I think that

1 what industry needs and what researchers need are guidance  
2 from the Agency about what kind of a viral load-driven NDA  
3 package would look like, and it is not just viral load.

4 There is questions about safety.

5 As Spencer mentioned, there is long-term followup,  
6 there is drugs like FIAU or [econite] or [fleconite] or  
7 high-dose clarithromycin where they have a great response to  
8 the marker and end up with excess mortality.

9 There need to be safety and activity information  
10 with other approved antiretrovirals and AIDS drugs as part  
11 of the approval package. We need to look at resistance,  
12 cross-resistance, long-term followup, sequencing of  
13 therapies, and consider, as Dr. Feigal just mentioned, the  
14 impact of resistance as a long-term safety issue even if the  
15 drug is benign in the short term.

16 We need to talk at some point, maybe not here, but  
17 maybe at a later workshop, about how long the monotherapy  
18 Phase I dose ranging safety and activity studies need to be  
19 and how we are going to compensate the brave volunteers who  
20 enroll for those Phase I studies which are going to probably  
21 foreclose future treatment options.

22 We also need to consider how we are going to  
23 retain CD4 as an important variable and define appropriate  
24 CD4 endpoints or switch points, and then finally, I think we

1 have learned some new things about the use of viral load in  
2 clinical practice over the last two days that may affect how  
3 the HHS panel that wrote the recent treatment guidelines is  
4 going to interpret the use of viral load, and we have  
5 learned that certain things, say, a one-month drop in RNA of  
6 one log may not be applicable to all patients, and we may  
7 need to want to go back to the HHS panel and ask them to  
8 slightly modify some of their guidelines for how to use  
9 viral load.

10 DR. HAMMER: Thank you.

11 Brenda.

12 MS. LEIN: Well, I guess that it has been echoed  
13 by a lot of the community folks that a trial design workshop  
14 is probably as important as this one, and a lot of the  
15 information that comes out of this, I think that the devil  
16 is going to be in the details, and I don't know how much we  
17 are going to be going into those, but as an advocate  
18 particularly for people with advanced stage disease, I  
19 haven't heard that much at this committee meeting, in the  
20 presentations, on the usefulness of viral load in predicting  
21 clinical outcome in people with very low T cells.

22 It is my understanding that CD4 changes are more  
23 clinically relevant in people with low T cells than viral  
24 load changes, and how that might fit into this discussion, I

1 think is also important.

2 DR. HAMMER: Thank you.

3 John.

4 DR. MODLIN: I don't have much. I think we have  
5 all gotten beyond the issue of if, and I think we really do  
6 need to be focusing on the details, and most of that is  
7 outlined in the questions that have been posed to the  
8 committee, and i think that is what we really need to be  
9 spending our time with.

10 DR. HAMMER: Joel.

11 DR. VERTER: I guess I will save most of my  
12 comments for the specific questions, but one theme that I  
13 would like to bring up is that I think that the gold  
14 standard of the randomized controlled clinical trials should  
15 not be lost in this discussion.

16 I admitted yesterday, and I will reiterate today,  
17 that I don't know all the data of these trials, but without  
18 seeing the clinical outcome data, I think we should be a bit  
19 cautious or I would advise the FDA, the committee, the  
20 community, and the companies to be cautious about proceeding  
21 with only a surrogate endpoint trial.

22 The streets of clinical trials are littered with  
23 surrogate endpoint trials that later prove to be--where the  
24 endpoint of surrogacy looked okay, but then the clinical

1 outcome was later proved to be either ineffective or even  
2 harmful, and I will try to make some comments during the  
3 discussion today.

4 DR. HAMMER: Thank you.  
5 Vernon.

6 DR. CHINCHILLI: Based on what we saw yesterday  
7 and today, I would have liked to have seen some more  
8 sophisticated statistical analyses correlating viral load  
9 with clinical endpoints, but given the consistency of  
10 results across a variety of data sets from various  
11 companies, I am pretty well convinced that this is the way  
12 to go, is to look at the viral load, and again, I will have  
13 some more specific comments when we get to design issues.

14 DR. HAMMER: Thank you.  
15 Wafaa.

16 DR. EL-SADR: I think I will save most of my  
17 comments until later. I guess I am a bit concerned that  
18 almost all the analyses presented to us focused on the  
19 responders, which is understandable since that is sort of  
20 what we are trying to get at with some of these future  
21 trials, but it would have been also very interesting to look  
22 in more detail at the nonresponders especially using viral  
23 load as an endpoint of nonresponse, and have analyzed that a  
24 bit more to try to identify maybe characteristics that may

1 predict nonresponse, and so on.

2 DR. HAMMER: Jim.

3 DR. LIPSKY: I will hold my comments until later.

4 DR. HAMMER: Judith.

5 DR. FEINBERG: I think most of the things that I  
6 am concerned about have been addressed by others, and I must  
7 say it is a delightful change from the indinavir/ritonavir  
8 meeting a little more than a year ago, to actually be  
9 approaching this question, because I think the data are  
10 pretty overwhelming that these are appropriate measurements  
11 of disease activity in the making.

12 I would say that I really also very much share  
13 Wafaa's concern about the other group, the sort of the  
14 forgotten group at this meeting, that those are actually, of  
15 course, the patients that the clinician agonizes over, and  
16 those are the people for whom management of this disease  
17 presents dilemma after dilemma, and it would be wonderful to  
18 try to tease out of these data sets what we could know about  
19 the group of people who don't do well.

20 DR. HAMMER: Chris.

21 DR. MATHEWS: No.

22 DR. HAMMER: Pamela.

23 DR. DIAZ: I will save most of my comments also,  
24 but to avoid being redundant, though, I would echo the

1 issues about the "forgotten" group as it was just mentioned,  
2 in particular those patients, if we are going to be setting  
3 clinical trials and very clearly wanting to know what  
4 constitutes or how long to wait to constitute a true  
5 response, if there is something about those who never will  
6 respond that one could identify much earlier on to enable  
7 them to get out of that trial and into something else, I  
8 think it would be very important to look at that data very  
9 carefully.

10 DR. HAMMER: Fred.

11 DR. VALENTINE: Although they are not mentioned in  
12 the questions the panel has been given, several speakers  
13 from the Agency have mentioned the concept that a label  
14 might be indicated that this drug or this combination of  
15 drugs is useful for dropping RNA copy number, and I can  
16 imagine that such a label could be written.

17 That is different from what is in the questions,  
18 however, and it is also, in my mind, different from saying  
19 that that drug has clinical utility for the overall syndrome  
20 of HIV disease.

21 It certainly is true, and we have seen lots of  
22 evidence in the last two days that we can treat replicating  
23 HIV by clearly the complications as has been mentioned that  
24 result in the immunodeficiency, and one would hope that we

1 also target those folks whose CD4 cells and whose function,  
2 something we are just now learning to measure, do not  
3 improve necessarily with dropping viral load.

4           So whatever labels read and whatever the approval  
5 process turns out to be, we want to make the distinction  
6 between treating the causative agent--which is certainly  
7 HIV--and correcting the clinical problem, which is  
8 immunodeficiency.

9           I also want to echo what Mark led off with, and  
10 that is that we are at a particular moment now in which  
11 guidelines have been written which are really quite  
12 incompatible in some of the recommendations with the data we  
13 have seen in the last two days, and I think that the  
14 committee really has to quickly add some corrections and  
15 some changes in that early decision point as listed in the  
16 recommendations.

17           DR. HAMMER: Thank you. I will just make a couple  
18 of brief comments. I certainly agree with the basic premise  
19 of this meeting, that thinking about new label indication of  
20 durable RNA suppression is appropriate, and an indication  
21 for traditional approval.

22           It goes without saying, however, that this disease  
23 in particular can't be approached simplistically, nor can  
24 the issue of a durable RNA suppression be so simply defined,

1 and it will be very interesting to see what this committee  
2 does with the first traditional approval if it sees it on  
3 this basis.

4           Speaking personally, we are going to want other  
5 things besides just a durable RNA suppression, of course.  
6 It has already been mentioned about CD4 responses. Some  
7 other issues, of course, are quality of life and other  
8 parameters, safety, drug interactions, and particularly  
9 resistance, the issue of burning bridges to other treatments  
10 are going to be particularly important.

11           I would also think that the design of these  
12 trials, when one thinks about it, has to have adequate  
13 numbers, and not just adequate numbers to power for RNA,  
14 because you can power studies for RNA in various ways and  
15 get relatively small numbers.

16           One has to think about what the numbers really  
17 have to be to illustrate, not just the minimal level of  
18 adequacy from a statistical power situation, but something  
19 that we would like to see in a traditional study leading to  
20 a traditional approval.

21           I think there are some cautionary notes here that  
22 came up in particular yesterday with Winston Cavert's  
23 comments, and that is the question of discordancy, whether  
24 there is discordancy between the plasma RNA response and the

1 lymphoid tissue with other compartments in particular, with  
2 the CD4 response. We need to know more about the proviral  
3 DNA and some interesting issues about at least levels of  
4 plasma RNA in the pediatric and adult populations.

5           One thing that has been brought up by a number of  
6 individuals, which I also would echo, is that a traditional  
7 approval based on durable RNA suppression, with it should  
8 come major commitments to Phase IV as far as safety is  
9 concerned and how to use these drugs.

10           We have talked about that before, and it is  
11 important to start putting that into reality as far as  
12 whether they are strategy trials, if you wish to call them  
13 that, but in particular, what to start with, what to change  
14 to, what the impact on other treatments is.

15           I would also support, whether it is this forum or  
16 another forum, yet another discussion about trial design.  
17 The FDA a couple of years ago had a very interesting  
18 symposium on trial design. It may be important to try to  
19 hold such another meeting. I don't think we will be able to  
20 really design trials this afternoon, but what has been  
21 discussed these past two days leads us into that direction.

22           With that, I would like to get to the specific  
23 discussion points that have been put toward the committee,  
24 and I am going to read this for the record. We will take

1 them in order.

2           There are three discussion points, two with  
3 subdivisions.

4           The first one is straightforward in its question,  
5 maybe not straightforward in its answer.

6           Does the available information support our  
7 conclusion that a durable reduction in plasma HIV RNA is  
8 evidence of clinical benefit?

9           I think I will start at my left, this end of the  
10 table, and start with Fred.

11           DR. VALENTINE: In reading this question, I  
12 actually, while I agree with the general consensus that we  
13 have seen lots of data that RNA decreases, the very large  
14 ones are associated with great clinical improvement, we all  
15 anecdotally have seen those changes in our patients, I was  
16 forced to cross out "is evidence of clinical benefit" and  
17 say that does the available evidence support our conclusion  
18 that a durable reduction of plasma HIV RNA predicts clinical  
19 benefit, and I think it most certainly does.

20           I guess I am just hung up on a laboratory change  
21 equaling clinical benefit. It certainly correlates very  
22 nicely and we have seen that, and I am convinced of that.

23           There is certainly strong evidence that drugs  
24 decrease RNA and that this is associated with improved

1 outcome for the infected individual.

2 So I am giving you my usual ambivalent answer.

3 DR. HAMMER: That is your prerogative as a former  
4 chair.

5 Pamela.

6 DR. DIAZ: Well, I would agree that there is  
7 certainly a substantial amount of evidence that would  
8 suggest that decreases in plasma HIV RNA correlates with  
9 clinical benefit. In terms of reading the question, I get  
10 hung up on the issue about durable reduction, and we will go  
11 on to describe and hopefully discuss that later on in terms  
12 of what really constitutes durable, but I would definitely  
13 agree that there is a lot of evidence to suggest that these  
14 two are correlated in terms of clinical benefit.

15 DR. MATHEWS: I think that a question and the  
16 discussion at these last couple of days really is based on a  
17 pathophysiologic model of HIV disease for which there is  
18 overwhelming evidence that the virus is what drives it all.

19 However, I think on an empirical basis, from the  
20 way we understand knowledge as it evolves in clinical trials  
21 and clinical practice, that we are doing a disservice by  
22 making a statement that simply a reduction in a laboratory  
23 test, which is an indirect marker of viral replication, of  
24 itself is clinical benefit, and I agree with Fred that we

1 should state what we mean, which is that there is evidence  
2 that it is predictive of clinical benefit.

3           Having said that, it is an incomplete predictor of  
4 clinical benefit. While in some of the Agency's  
5 presentations, it was explicitly stated that this discussion  
6 is not about the ultimate validation of the surrogacy of  
7 this marker or any other, I think from a clinical point of  
8 view, one wants to know to what extent the changes predict  
9 and have particular interest in the populations of people  
10 for whom the marker does not predict well.

11           So, having said that, my conclusion is that  
12 definitely, RNA can be included as the major component of a  
13 new primary endpoint for clinical trials of antiretroviral  
14 agents, but that I feel quite strongly that CD4 responses  
15 need to be included in that definition of a primary  
16 endpoint.

17           DR. HAMMER: Thank you.

18           Judith.

19           DR. FEINBERG: Well, I would say that to a large  
20 extent I agree with many of the speakers that have preceded  
21 me, so in the interests of time I won't agonize over that.  
22 I am struck by the fact that in certainly the indinavir data  
23 set, that there were patients who ultimately responded, but  
24 whose viral load was still detectable out to approaching six

1 months, and that I share Pamela's concern about the use of  
2 the word durable in this sentence since the data sets  
3 presented to us are barely twice that duration, in other  
4 words, the followup that was prepared as part of this  
5 meeting really I don't think any of the data sets went  
6 beyond 48 or 52 weeks, and so I think durable is kind of to  
7 me a word in quotation marks.

8           It is certainly enough of an indication that  
9 things are moving in the right direction in terms of  
10 treatment, but, you know, like Pamela, I take issue with  
11 that word, and I agree with Chris and Fred about the  
12 predictive part. I think that is a more appropriate way to  
13 phrase it.

14           DR. HAMMER: Thank you.

15           Jim.

16           DR. LIPSKY: In its broad, sweeping context, the  
17 data do support that it is predictive of clinical benefit.  
18 The problem again is in the details. There is no definition  
19 of durable, there is no definition of reduction, and the  
20 clinical benefit is not defined, but despite all of that--

21           DR. HAMMER: You are going to get an opportunity  
22 to define that in the next question.

23           DR. LIPSKY: That comes later, but one wonders if  
24 the cart isn't before the horse.

1 DR. EL-SADR: The data I think are there to  
2 support using plasma HIV RNA for regulatory purposes as an  
3 endpoint for approving antiviral drugs. I think the  
4 sweeping statement is a little bit of concern, and I think  
5 it is taking a whole other sort of leap forward, but I think  
6 we can move ahead with the discussion because I am in  
7 agreement that we should move on and discuss using plasma  
8 HIV RNA as an valid endpoint for our trial.

9 I have trouble sort of supporting the broad  
10 statement as stated.

11 DR. HAMMER: Vernon.

12 DR. CHINCHILLI: Yes, I believe there is evidence  
13 of a correlation.

14 DR. HAMMER: Joel.

15 DR. VERTER: Can I be permitted two or three  
16 minutes to explain?

17 DR. HAMMER: Oh, sure.

18 DR. VERTER: I actually agree with the initial  
19 statements about using the word predictive or associated. I  
20 support that fully. I think back when I get into situations  
21 like this to a phrase from my graduate days, and that is  
22 what is the question.

23 I think in the multitude of studies and data that  
24 we have been presented, the question is can studies identify

1 "responders," and if so, can these studies then be used to  
2 estimate time to response, time to relapse, if you will,  
3 time to clinical endpoints. Then, the answer is probably  
4 yes.

5           However, in order to answer that yes, you have to  
6 appropriately define responder, and it has to be some  
7 consistent definition across studies, and the methodology  
8 used has to be consistently applied, and I am not sure that  
9 that was done in all these studies, and that may be due to  
10 the limitations of the design and the resource available,  
11 but for the FDA, the community, and the companies, I would  
12 advise a few points.

13           One, I don't support looking at a meta-analysis  
14 right away, so those studies that were combined in the  
15 presentation I think should be presented to the FDA as  
16 individual studies, so they can look at the individual  
17 design issues, the cohort studies, the drugs used, and  
18 things of that nature. Then, if they want to do some  
19 overview, I think that would be fine, but to do it  
20 initially, I think is a mistake.

21           Second, from the vast number of slides that went  
22 by, I think I detected a lot of missing data, patients who  
23 started out as responders, you know, like there were 90, but  
24 then at some point there were only 65 reported, and don't

1 quote the numbers because I don't remember all the numbers,  
2 but I think you need to take a very careful look at what the  
3 cohort was at the beginning, what it was at the analysis,  
4 and what happened to those people in the middle.

5           If people were responders initially, but they were  
6 missing data and couldn't be included, that may be evidence  
7 of some selection bias, which may enhance the effect or it  
8 may completely wipe out the effect, and I think you need to  
9 take a look at that very carefully.

10           Then, if possible, I think, as I mentioned before,  
11 you should try to get the companies to use as similar a  
12 definition of response as possible, whether it is 400 for  
13 the viral load, I am sorry, for the--the viral load, I  
14 guess, I probably get my terms mixed up, but you know what I  
15 mean--there needs to be some consistency. If you are going  
16 to try to use a surrogate for all drugs that come by, then,  
17 you should have some reasonable assurance that that  
18 definition of surrogacy was used comparably across the  
19 studies, or at least that there was consistency across the  
20 studies.

21           Finally, I would say one other thing about that,  
22 and then also the thing was mentioned about durability of  
23 reduction, something about how that is defined also, was the  
24 same methodology used, the amount of the reduction, and the

1 length of time that you are going to use, one month, four  
2 months, six months.

3           Finally, I think I agree with others that have  
4 said this, there has to be some better analyses about the  
5 surrogacy and its relationship to the clinical outcome. I  
6 hope that everyone would agree that it is to the benefit of  
7 everyone that if there is no clinical relationship to the  
8 surrogacy, then, the surrogate is worthless.

9           If all you are doing is reducing a count, but  
10 mortality is still increased, side effects are higher,  
11 morbidity is worse, then, the surrogate should be worthless,  
12 and so there has to be very careful looks at the  
13 relationship of the surrogacy to the response, and there you  
14 could get into serious statistical and analytic problems  
15 because you need to get into some sort of selection bias,  
16 what is a response, what is not, does that introduce some  
17 better health group that is more likely to have clinical  
18 benefit.

19           So, there I would hope that as was also mentioned  
20 before, you can go back and look at all the "nonresponders"  
21 and see their clinical outcomes also, and get back into  
22 that. That has to reflect with the sensitivity and  
23 specificity of the tests, the surrogate, the outcome, and I  
24 am sure I don't have to discuss that with the FDA, I am sure

1 they are all too well aware of that.

2 DR. HAMMER: Thank you.

3 John.

4 DR. MODLIN: I don't differ much from the comments  
5 that have already been presented by most of those preceding  
6 me, in fact, I think I am going to save most of what I have  
7 to say when we get to discussing the pediatric issue, Scott.

8 DR. HAMMER: Okay.

9 Brenda.

10 MS. LEIN: I echo a lot of the concerns, and I  
11 think that I want to discuss the details, so I will just go  
12 forward.

13 DR. HAMMER: Mark.

14 MR. HARRINGTON: Like Fred, I would have liked to  
15 remove the word "evidence" and replace it with "strongly  
16 predictive."

17 I want to talk about the discordant patients for a  
18 couple minutes. I hope that the approval standard doesn't  
19 just become a way for drug companies to get really rotten  
20 drugs or drugs that were studied in rotten combinations  
21 approved, and I am referring to studies like Upjohn 021 and  
22 017, where there was significant viral load difference of  
23 0.4 log between nucleoside monotherapy arm and the AZT or  
24 DDI plus delavirdine arms, and yet there was no clinical

1 benefit.

2 I would also like to refer back to the DDC  
3 experience with DDC monotherapy, naive patients, 114,  
4 experienced patients, 119 in combo therapy with ACT and DDC  
5 and 155. There is a certain viral load reduction which can  
6 be statistically significant and won't be clinically  
7 significant, and so we wouldn't want sponsors to allow  
8 companies to just show any reduction at all and come in for  
9 approval, so they would have to have an incentive to study  
10 the drug in the most potent and the most optimal regimen,  
11 which would mean I would hope the committee or the FDA would  
12 come out with a strong statement against incestuous  
13 combinations of polytherapy from a single sponsor, and again  
14 still have optimal control arms.

15 DR. HAMMER: Thank you. I will just add a brief  
16 note. The question asks about what the available  
17 information supports, and what the available information  
18 supports is that short-term changes, basically, changes in 4  
19 to 24 weeks after starting therapy are strongly associated  
20 with improvement in clinical benefit, but responses beyond  
21 that, as far as prediction for clinical benefit, is a  
22 logical conclusion, but we still have precious little data  
23 about that just because it hasn't been developed, so I think  
24 what we have is extraordinarily strong data about 4 to 24-

1 week responses and what that predicts for later on.

2           It is a reasonable and logical conclusion and  
3 deduction to suggest that more durable suppression beyond  
4 that point will lead to further clinical benefit, and I  
5 support that hypothesis, but the available data really are  
6 fragmentary in that regard. That is I think what will be  
7 generated over the next couple of years.

8           Moving on to the second question, there are four  
9 parts to this question. I will read it for the record. I  
10 will ask that each of the panelists really, if you would, to  
11 save time and to be efficient, to comment on Parts A, B, C,  
12 and D in your responses.

13           Question 2 or Point 2. For the purpose of  
14 evaluating drug efficacy:

15           A. What is the most appropriate definition of a  
16 clinically meaningful virological response?

17           B. Should the definition differ for specific  
18 subpopulations such as children, antiretroviral experienced  
19 patients or baseline disease status?

20           C. Given this definition what would constitute a  
21 loss of that response?

22           D. How long should responders be followed to  
23 assess a durable virologic response?

24           I will start at this end. Mark, do you want to

1 start?

2 MR. HARRINGTON: All four at once? Okay.

3 DR. HAMMER: Judith has a suggestion to do A and B  
4 first, and then C and D later. I feel not strongly about  
5 either approach.

6 MR. HARRINGTON: Well, for A, I don't think the  
7 FDA has distinguished clearly enough between the need for  
8 small, and hopefully as small as possible, monotherapy Phase  
9 I dose ranging studies to find an active dose and to find  
10 maximum tolerated dose and safety.

11 Then, the studies that will lead to accelerated  
12 approval where I think the virological endpoint would need  
13 to be proportion of people undetectable at week 24 or for  
14 accelerated, week 48 for full approval in an appropriate  
15 combination regimen, and that is not really quite spelled  
16 out here. I assume the FDA was thinking in terms of data.

17 The third endpoint, which would be for the  
18 postmarketing followup, would be the duration or the  
19 proportion, say, the median duration of people that remained  
20 undetectable, for how long, or median time to failure.

21 As far as B goes, should the definition differ for  
22 specific subpopulations, I feel that we lack information to  
23 say that the definition should definitely differ, but I  
24 think that we should insist that those groups of children,

1 experienced patients, and multiply-resistant patients, and  
2 people with advanced AIDS are all included in the package,  
3 and that we don't just go study pristine antiretroviral  
4 naive patients.

5 DR. HAMMER: Thank you.

6 Brenda.

7 MS. LEIN: I guess that I would add that I think  
8 that the definition probably does need to differ between  
9 different specific subpopulations, especially those people  
10 who are extensively antiretroviral experienced.

11 I think part of the information that is missing in  
12 patient and physician decisionmaking is the percent of  
13 people who have prior antiretroviral experience for whom  
14 this drug is active.

15 Something that might work quite well in a naive  
16 population may be inappropriate for someone more advanced,  
17 and the only way that we can really tell if that group of  
18 people aren't achieving below the limit of detection, if we  
19 also collect data across studies on the percentage of people  
20 for whom the drug is active even if they are not achieving  
21 below the limit of detection.

22 I think that then what is an appropriate  
23 definition for a clinically meaningful response would vary  
24 depending on the population that you are looking at.

1 DR. MURRAY: Could I ask a question of the  
2 responders? When you are talking about the limit of  
3 detection, I guess we want to just remind you that there is  
4 not one limit of detection, and so if you have a feeling  
5 about a certain limit of detection that you would like to  
6 see in clinical trials, you might want to comment on that,  
7 too.

8 MS. LEIN: Well, I thought that there was a limit  
9 of detection, and there was a limit of quantification, and I  
10 am not sure that they are not static.

11 MR. HARRINGTON: I felt like the data that we saw  
12 indicated that we should probably use the more sensitive  
13 assays for research purposes, but that for clinical  
14 management, 400 appears to rapidly predict a group that is  
15 going to--if you go back above 400, like in the nevirapine  
16 study, you are rapidly going to go back up anyway. So I am  
17 comfortable with using that as the current definition of a  
18 clinical undetectable or limit of clinically relevant  
19 detection, although I think that industry needs to work on  
20 the more sensitive assays. I don't think they are ready for  
21 prime time.

22 DR. HAMMER: John

23 DR. MODLIN: Just to respond to Jeff's question  
24 first, I would certainly encourage the use of the most

1 sensitive method available for the purposes of clinical  
2 trials. I think inevitably you are going to learn more in  
3 the long run about not only the effect of these drugs, but  
4 also a little bit about the pathogenesis of disease if you  
5 insist on using the most sensitive assay that you have  
6 available.

7           With respect to the first, Subpart A, what is the  
8 most appropriate definition of clinically meaningful  
9 virological response, I think we have pretty reasonable or  
10 we are seeing pretty reasonable data, that if you are  
11 talking about a change from baseline, that a response of  
12 something over a half a log seems to correlate pretty nicely  
13 with clinical benefit.

14           There even is a little bit of data from the ACTG-  
15 300 trial, where we heard very little information, but  
16 changes in baseline as little as 0.7 to 0.9 logs is  
17 associated with the clinical benefit in that pediatric  
18 population.

19           However, I don't think you can apply the same  
20 standard when you are actually comparing two different arms  
21 and you are looking at differences between those arms, and  
22 again I would remind you that both ACTG-152 and 175 had arms  
23 in which they demonstrated differences of approximately half  
24 a log between RNA levels between two groups for which there

1 was no clinical benefit derived or difference that was  
2 observed between those two groups, and so it depends on how  
3 you are applying the yardstick in terms of just exactly what  
4 the definition ought to be.

5           Let me move on and just make a few comments about  
6 this question as they relate to pediatric trials. We  
7 obviously don't have the same wealth of data in the  
8 pediatric populations as we have been privileged to hear  
9 from adult trials over the last two days.

10           Secondly, the natural history of this disease is  
11 different in children although--well, it is different  
12 because, number one, as we have heard, kids tend to have  
13 higher viral loads from the very beginning than adults do.  
14 They also have higher CD4 cell counts, and in fact, there  
15 may be a relation between those two phenomenon and that the  
16 more CD4 cells you have to replicate virus, the higher the  
17 viral load may be.

18           I don't think we know that, and I think it would  
19 be very interesting to correct some of the pediatric viral  
20 load data for CD4 cell counts to see if the figures that you  
21 get don't correspond a little more closely to what we have  
22 seen with adult data.

23           Nonetheless, children probably do progress more  
24 rapidly. They have a shorter natural history. They

1 progress to endpoints more rapidly. Granted, the endpoints  
2 that the pediatric trials have used are different than what  
3 adult trials have used, and many of the endpoints have been  
4 weight loss, changes in neurological function, cognitive  
5 function or both.

6           Even with that caveat, I think most of us believe  
7 that the natural history of the disease is foreshortened in  
8 pediatric patients compared to adult patients. Nonetheless,  
9 it is the same virus. It is largely the same disease as in  
10 adults, and I think it is reasonable to expect that control  
11 of the virus in children or control of viral replication in  
12 children will lead to the same clinical benefits that  
13 control of viral replication in adults has obviously been  
14 demonstrated to do.

15           I think the little bit of information that we  
16 heard yesterday from both ACTG-152 and very preliminary  
17 information from ACTG-300, it would tend to corroborate this  
18 impression.

19           Even though we have less evidence, I think I would  
20 encourage the Agency to support the design and conduct of  
21 pediatric trials that do have virologic endpoints. I think  
22 they are likely to provide a greater degree of confidence in  
23 these antiviral agents than in the past where we have  
24 approved these drugs for use in children based on efficacy

1 data from adults only.

2           Again, I think virologic endpoints may actually  
3 provide a more precise indication of the effectiveness of  
4 these drugs in children. This is going to be particularly  
5 important since now we are down to a point where with an  
6 overall vertical transmission rate in a range of 5 percent,  
7 the numbers of children that are going to be available for  
8 pediatric trials in the not too distant future is going to  
9 decline pretty dramatically, so anything we can do to get  
10 good--we call them surrogate endpoints, I am not sure I  
11 really view viral load markers as a surrogate--but,  
12 nonetheless, it almost seems as if the pediatric population  
13 would be an ideal population in which to use these  
14 endpoints.

15           Children begin with higher RNA levels and  
16 therefore it may not be reasonable to consider a fall  
17 beneath the least detectable level to be a necessary  
18 clinical response. I don't think we know that yet. We are  
19 just going to have to wait and see what the outcome of the  
20 current trials are with the protease inhibitors in children.

21           Unfortunately, we just aren't at the same point  
22 that we are with adults, and of course, the reason for that  
23 is, is that the opportunities to test these drugs in  
24 children have been delayed way beyond the point where we are

1 with adults at the moment.

2           So, it may be that with children having higher  
3 viral loads to begin with, we are probably going to have to  
4 examine just what the most appropriate metric may be in  
5 terms of most appropriate viral load metric may be as a  
6 principal or a primary outcome measurement.

7           It may need to be a certain drop, a 2 log drop, or  
8 1.5 or 2 log drop as an example, as opposed to a drop down  
9 to levels that are undetectable, that, of course, combined  
10 with some measure of duration.

11           But I guess my bottom line is I view this as a  
12 welcome change from a pediatric standpoint, and certainly  
13 would encourage the Agency to continue in this direction.

14           DR. HAMMER: Thank you.

15           Joel.

16           DR. VERTER: I guess to me the issue is one of  
17 analysis and design. I don't think that we saw a lot of  
18 data which would lead me to give you at least a statistical,  
19 if not a medical suggestion of what it is.

20           I mean the response is a continuum, and if  
21 anything, what we saw are cuts, a half a log or 1.5 logs or  
22 2 logs. I am not sure that I believe there are too many  
23 biological mechanisms which have absolute cuts and above one  
24 you are good and below one you are bad. It is much more of

1 a continuum.

2           So, I guess the only thing I could do is suggest  
3 to the Agency and the companies to try to put together an  
4 appropriate analytic program which would look at the data  
5 available to see if, indeed, there is a cut or whether it  
6 should be more of a continuum, and specifically, you know,  
7 how that cut or continuum relates to specific outcomes,  
8 mortality, morbidity, or quality of life.

9           DR. HAMMER: Thank you.

10          Vernon.

11          DR. CHINCHILLI: I guess one of the issues that  
12 concerns me about the viral load is this rebound effect that  
13 occurs after there is a successful response, and I don't  
14 understand whether or not--and we probably won't answer  
15 this--but what I don't understand is, is it beneficial to  
16 the patient, say, who is at a certain baseline level, and  
17 then the treatment has a successful effect, and the patient  
18 gets down to below detectable levels, and then you see the  
19 rebound effect that Dr. Elashoff demonstrated.

20                 Maybe the patient doesn't come all the way back up  
21 to baseline levels, but is the patient better off, and this  
22 relates to what Joel was asking, is should we keep this on a  
23 quantitative continuum level in terms of even if there is a  
24 slight reduction in the person's viral load, is that

1 beneficial to the patient, or do you really just have to get  
2 it down there really low for it to be beneficial.

3           If you really have to get it down there to be low  
4 for it to be beneficial, and keep it there, then I think I  
5 agree with the Agency's approach, and that is treating it as  
6 a time to event occurrence.

7           If even slight reductions or even moderate  
8 reductions in the viral load after the rebound are  
9 beneficial to the patient, then, probably we should keep it  
10 on a continuum. So, I agree with Joel that this issue I  
11 think hasn't been fully settled.

12           It wasn't clear to me after all the discussions  
13 today and all the data sets, since everybody analyzed them  
14 differently, what is the proportion of people who undergo  
15 this rebound effect. Obviously, we can't answer that given  
16 the multitude of treatments that were assigned and the way  
17 the different analyses were performed.

18           So those are some of the initial questions I had  
19 to bring to the table.

20           DR. HAMMER: Thank you.

21           Wafaa.

22           DR. EL-SADR: I think the definition of most  
23 appropriate virologic response really depends on the  
24 population that one is looking at, and I think it will be

1 the expectations of--my expectations of a virologic response  
2 differ whether it's a virologically naive antiretroviral  
3 naive group versus a very experienced group that has failed  
4 other drugs, as well as also maybe some other parameters  
5 that involve other populations, so it is very difficult to  
6 come up with one definition that would apply to all the  
7 different populations and subpopulations that would be  
8 eligible for these studies.

9 I also think that all the data we saw reflected  
10 primarily individuals with median CD4 about 200, and I don't  
11 know--maybe somebody else knows--but I don't know if we have  
12 any idea whether similar responses in individuals with  
13 higher CD4 with early HIV disease are reflected with a  
14 clinical benefit.

15 I think it is an unknown, so I think again it  
16 really depends on the population in whom the drug is going  
17 to be tested and the expectations of an activity of a drug  
18 in that population, whether it be naive or experienced.

19 Another subpopulation that seems to be missing  
20 here is women, and I think for a variety of reasons, I think  
21 women are an important subpopulation to look at primarily  
22 because there are different manifestations of HIV.  
23 Certainly, wasting is different in women, and also maybe the  
24 drug/drug interactions, they are on different medications,

1 the side effect profile may be different, as well, so I  
2 think that is another important population to be included.

3           One issue, I guess when I am thinking of a  
4 meaningful virologic response, I think of a composite  
5 response rather than one thing, and the composite response  
6 may be in a population that is very antiretroviral  
7 experienced, maybe drop to some level, half a log or  
8 whatever, in that population versus a naive group where you  
9 really are going for a durable effect below detectable  
10 level, the most sensitive assay probably is best to be used  
11 in clinical trials.

12           Included in that composite response, I think the  
13 duration of the suppression, the level of suppression may be  
14 more valuable as an endpoint in an experienced group, as I  
15 mentioned before, but maybe the rapidity of the response may  
16 also be another virologic marker that may be important in a  
17 subpopulation, as well, and I think then the other component  
18 of this composite response that I am thinking of is  
19 resistance, and I think we cannot sort of ignore resistance,  
20 and maybe the proportion of responders or nonresponders who  
21 become resistant to that drug may be part of our sort of  
22 composite virological endpoint that is clinically meaningful  
23 to me in looking at a new drug.

24           It is hard to sort of think of a virologically

1 meaningful endpoint without having some component there that  
2 says it should not be associated with a deleterious effect  
3 on the CD4 count, so somehow within that virologic response  
4 there should be at least a maintenance or sustained or  
5 something CD4 response, as well, because we certainly don't  
6 want an antiretroviral drug that is very active against the  
7 virus, but lyses all the CD4 cells.

8           So, in essence, I think more in terms of composite  
9 virological response variables that can be then adjusted to  
10 each subpopulation as appropriate.

11           DR. HAMMER: Thank you.

12           Jim.

13           DR. LIPSKY: To answer the first question what is  
14 the most appropriate definition of a clinically meaningful  
15 virological response, I think two things have to be  
16 addressed - number one, the assay characteristics, and  
17 second, what is the data which we saw.

18           First, on the assay characteristics, we were  
19 presented information yesterday at least at the high, and  
20 not the ultra-sensitive, that meaningful information from an  
21 assay would come if there was a drop of greater than 0.5  
22 logs, I think even the stretch was to around 0.7, so that  
23 has to be taken into consideration.

24           That being said, what happens when viral load

1 dropped. We did see data I believe yesterday that was on a  
2 continuum, and we saw a fair amount of it, and there was, in  
3 aggregate, pretty impressive data that has viral load  
4 decreased, clinical benefit increased, and indeed detection,  
5 that effect was detected even at the most sensitive levels  
6 of drop based on what I described as the characteristics of  
7 the assay, that is, I believe in levels of decrease in viral  
8 load of a half a log, benefit was detected or improvement,  
9 and again definitions given weren't clear. I think, what,  
10 in 37 percent of the patients, things got better as you went  
11 down.

12           Now, that certainly was in aggregate, and that  
13 looks encouraging, so one could say that the most  
14 appropriate definition of a clinically meaningful  
15 virological response would be that greater than 0.5, maybe  
16 0.7 logs, because that appears to be in aggregate what we  
17 saw, but what about specific subpopulations?

18           It was good to see the data in children, which has  
19 already been mentioned, and indeed there was benefit  
20 attributed to a log drop, which I think you quoted  
21 correctly, my notes show 0.7, 0.9 log units, so that is  
22 certainly consistent with the adult population and would fit  
23 in with a drop of greater than a half a log.

24           When you get down to definition differing for

1 antiretroviral experienced patients or baseline disease  
2 status, that is a bit more problematic when you look at the  
3 specifics, and we probably do not have enough data or at  
4 least maybe that we do have, but it wasn't presented, to be  
5 clear on what should be done.

6           For example, the data presented from the Harvard  
7 School of Public Health yesterday showed that intriguing  
8 Kaplan-Meier plot where those patients who had lower initial  
9 viral loads, baselines greater than 55,000, which in other  
10 studies wasn't that low, but anyway, that the greatest  
11 predictor of how they did and not progressing was the  
12 overall viral load, and that is, their viral at the  
13 beginning, and indeed those that even had viral levels  
14 greater than baseline at--if I am reading the graph  
15 correctly--at 24 weeks, clinically, did better.

16           So that is intriguing, but what that means is that  
17 I think we need more data to know clearly how definitions  
18 can be modified, but that is not to take away just, you  
19 know, that single finding, the overall fact that, yes, if  
20 you get a meaningful reduction in virus, which is less than  
21 a half a log, in aggregate, patients are going to do better.

22           The question was brought up what about at the  
23 other end for ultra-sensitive assays of 50 copies, 20  
24 copies, or below, or going, as we heard from Roche, perhaps

1 not meaningfully quantitatively able to get an answer, but  
2 qualitatively knowing that the virus is there, what is the  
3 answer there?

4           Again, I would say that perhaps this may be the  
5 one of the more intriguing aspects of therapy, you know,  
6 what is the answer when you have very low amounts of virus,  
7 what does that mean? I think we need to know more.

8           It looks like from the data that we have, the  
9 lower you are, the better off you are, but what does it mean  
10 to have virus present at all, and I think more data needs to  
11 be learned from that.

12           Again, we also have to realize that we are  
13 measuring virus in the serum, on the plasma, and we were  
14 warned and we all know that this is just one of many body  
15 compartments, and this may certainly be predictive of  
16 eventual outcome. Certainly, in cancer chemotherapy, it was  
17 learned that the CNS was a protected area, until that was  
18 treated, certain leukemias didn't get better.

19           Also, there is, of course, an analogy to cancer  
20 therapy that we are finding again in hematologic  
21 malignancies, that with ultra-sensitive assays, remissions  
22 may not be as complete as what we think, but again,  
23 detection may not necessarily being progression of disease  
24 or return of disease, but I think what we are being told is

1 that we need to know more at that end of the spectrum.

2 DR. HAMMER: Thank you.

3 Judith.

4 DR. FEINBERG: Well, Wafaa and I had breakfast  
5 together and maybe there was something in the coffee because  
6 I think my responses are going to sound very parallel to  
7 hers.

8 Starting with this whole concept of what is the  
9 most appropriate definition, I guess once again I think I  
10 take issue with the wording, because to me the most  
11 appropriate definition would include both magnitude and  
12 duration of response, and here, we have been asked to  
13 address these as separate concepts.

14 So in my mind, it would be not only having an  
15 impact on viral replication, but that that impact could be  
16 sustained for specific periods of time, but if you just  
17 think of it in the short term, you know, just the way the  
18 question is phrased, what would be an appropriate  
19 definition, then, you know, I am in Wafaa's camp.

20 I think that percent below the limit of detection,  
21 you know, is a start and might be a perfectly reasonable and  
22 sensitive way to assess the response of any retroviral naive  
23 patients to therapy, but it is really very clear from all  
24 the analyses we have seen, as well as from our clinical

1 experience, that baseline characteristics have a predictive  
2 value for how people are going to respond, in particular,  
3 people who are heavily pretreated, which may be just another  
4 way of saying that either one or both, that they have very  
5 high viral loads, so that they have a fair degree of  
6 resistance before you put them in your new protocol for the  
7 next wonder drug, and I think for these individuals, how you  
8 would define virologic response would really be different.

9           I guess I would argue--I haven't got quite as far  
10 in my thinking as the idea of a composite or aggregate  
11 endpoint, but I certainly got as far enough to think that  
12 there is more than one appropriate definition, not what is  
13 the most appropriate definition, that I don't see this being  
14 so readily divorced from the population you are treating.

15           I do really think that you would need population-  
16 dependent analyses, and since, in fact, we are so early in  
17 the life of learning how to measure all these things and  
18 define what we are talking about, I think it would actually  
19 be premature to settle on only one definition. I think that  
20 would be a mistake.

21           Now, whether it would be reasonable or possible to  
22 combine several measures into an aggregate endpoint, I am  
23 not sure about and I haven't given that thought until Wafaa  
24 raised it, but I think that might be something we would want

1 to consider, specifically for people who are heavily  
2 pretreated or start with viral loads in the high hundred  
3 thousands or over a million, you know, it might be perfectly  
4 reasonable to talk about either a specific log change, which  
5 I think based on yesterday's discussion, in my mind would be  
6 at least--it would have to be more than half a log, because  
7 you would need to be considering the concerns about assay  
8 variability or perhaps even better, a rate of change over a  
9 defined time interval, so that you would feel that you had  
10 the possibility of providing what you would hope would  
11 correlate to some clinical benefit for people for whom  
12 achieving a value of HIV RNA below a limit of detection is  
13 not realistic, and is not maybe even biologically  
14 achievable.

15           So I would think that we would need a number of  
16 different measures that, to some extent, they would be  
17 population dependent, and that even in the best prognosis  
18 group, people with modest viral loads and no pretreatment  
19 history, even there I would think that it would be valuable  
20 to use a number of different approaches, so that we could  
21 begin to tease out over the next several years what exactly  
22 is going on as we intervene with treatment in the  
23 pathophysiology of this disease.

24           I guess the other issue that Jeff wanted us to

1 address was which level of detection or how ultra-sensitive  
2 should the assays be, and I don't know that I have again one  
3 clear answer on this.

4           It is clear that the less than 400 or 500,  
5 depending on which company's presentation it was, and the  
6 less than 50 or 20 track in parallel although the time  
7 course is different, I think because there were in every  
8 company's analysis patients who did not achieve the defined  
9 undetectable limit at the earliest time point that trials  
10 ought to be structured to give a benefit of a doubt, and  
11 maybe it would be useful to look at both an ultra-direct and  
12 a standard assay to keep reassuring ourselves that we are  
13 learning more and more of what we can from these patient  
14 populations.

15           I am very worried about the definition of a  
16 clinically meaningful virologic response that comes too  
17 early in the course of treatment, I think not only in trial  
18 designs and drug development, but then in general clinical  
19 practice we would do people a big disservice by abandoning a  
20 potentially useful regimen far too early, and there is no  
21 question that patients that burn out their options in a  
22 hurry if you do that.

23           So I guess I am on the fence about which assay,  
24 you know, to have to choose one over the other. I am not

1 sure I have a clear sense of what would be best, but only  
2 that we would think about the time to that limit as being an  
3 important variable to think about in the trial design.

4 DR. HAMMER: Thank you.

5 Chris.

6 DR. MATHEWS: I think the proposal that the Agency  
7 seem to be most comfortable with as the proportion of people  
8 who are undetectable at a given time point is a good  
9 criterion for a meaningful virologic response in the sense  
10 that it is in all that we have looked at, perhaps the most  
11 rigorous and makes the most sense in terms of our  
12 understanding of the pathophysiology of the natural history  
13 of the disease, specifically, if you can shut off viral  
14 replication and keep it shut off, you permanently alter the  
15 natural history of the disease for those patients.

16 I was impressed with the kind of data that was  
17 illustrated in the INCUS trial data presented today, that in  
18 terms of duration of response, you really had to have  
19 evidence of very low levels of viral replication in that one  
20 particular study was less than 20 was the cutoff, and if you  
21 didn't achieve that, it didn't matter if you were using a  
22 cutoff of 20 or more.

23 On the other hand, I am concerned that applying  
24 that kind of a criterion may have the unfortunate effect of

1 discouraging trials in advanced disease patients and in  
2 patients who are heavily pretreated, for whom that kind of  
3 outcome may not be common.

4           Therefore, I was actually in quite a bit of  
5 agreement with our visiting statisticians on viewing the  
6 response as a continuous response over time, because in  
7 fact, you know, you were showing curves of responses for  
8 individual patients, and in a sense it is artifactual to  
9 just say we are going to look at a fixed time and see the  
10 percentage of people who are below a certain cutoff, when,  
11 in fact, you have repeated measures that are generating very  
12 interesting patterns, and they are all very different.

13           So, I could conceive of trials, particularly in  
14 the more difficult populations to treat, who have few  
15 options, where you would be using model-based analyses of  
16 the patterns of response over a particular period of time.  
17 The slopes have declined over the first 20 to 24 weeks, and  
18 so on, in those kinds of populations, and that in more early  
19 patients, or populations who have not been heavily  
20 pretreated, to impose a very rigorous criterion using the  
21 most sensitive assays available.

22           DR. HAMMER: Thank you.

23           Pamela.

24           DR. DIAZ: In terms of answering the question what

1 is the most appropriate definition of a clinically  
2 meaningful virologic response, I, too, have difficulties  
3 answering that question without diverging down to Part B,  
4 which is defining the definition in terms of different  
5 populations, because I have differing thoughts about those  
6 specific populations in terms of what is perhaps clinically  
7 meaningful, but before I address those issues, in  
8 particular, I would like to diverge and take the word  
9 "clinically" out of Part A and just make a comment that has  
10 already been made, I believe, about what is a meaningful  
11 virologic response.

12 I just want to reiterate that based on the fact  
13 that the data that has been presented would suggest that  
14 certainly with the Roche assay, the licensed Roche assay  
15 that all that data would suggest that about a 0.5, maybe 0.7  
16 log difference would be considered to be a meaningful drop  
17 based upon the limitations of the tests from the standpoint  
18 of inter-assay differences, and I think that is extremely  
19 important, not so much additionally for designing clinical  
20 trials, but based on what will be used on the outside by  
21 clinicians to define a person who is responding and that  
22 despite the fact that it is not the Agency's prerogative to  
23 control laboratories and control labs in terms of their  
24 assay accountability, the message has to be very clear that

1 this is extremely important in ensuring that when this test  
2 is used clinically, that people understand the limitations  
3 of the particular laboratory.

4           With that said, though, I would move to the issues  
5 about what is clinically meaningful and specifically  
6 comment. I would base my comments based on what is  
7 clinically meaningful in terms of what is meaningful from  
8 upfront in term of a drop in viral load.

9           I would agree with a prior statement that  
10 certainly control of viral replication, and any group should  
11 really be a goal, but at this point, what is attainable with  
12 current therapy needs to be taken into account, and I think  
13 that specifically in terms of designing trials and, in  
14 particular, in terms of licensing products, that we have to  
15 realize that what is clinically meaningful is a very dynamic  
16 process and that what we see over time and what we get in  
17 terms of clinical data over time may modify our definition  
18 of what we ultimately consider to be clinically meaningful.

19           In terms of just a couple comments about pediatric  
20 patients in particular, I would just make the comment that I  
21 think we need to have some of the data available in  
22 pediatrics with the use of protease inhibitors in particular  
23 to be able to make that definition for that particular  
24 population, and that in addition, in designing trials for

1 pediatric patients that based on the natural history and  
2 some of the viral load data that has been recently published  
3 in Pediatrics, we may have to have different definitions of  
4 what is clinically meaningful for even different age groups  
5 of children, in particular, neonates versus older children  
6 when we do design trials.

7 DR. HAMMER: Thank you.

8 Fred.

9 DR. VALENTINE: The definition of the meaning of  
10 virologic response may well differ for Phase I studies and  
11 for licensing trials. Durability is clearly an issue in  
12 both cases, and I think that, as Mark Harrington alluded to,  
13 how long a Phase I trial in which you are defining dose,  
14 determining virological effects, and determining some short-  
15 term toxicities is going to become increasingly difficult.

16 The duration that I would say needs to be done is  
17 probably a minimum of 12 weeks or so, although this raises  
18 real issues, and there are going to be tremendous problems  
19 which are not directly addressed by this question, problems  
20 in the great amount of cooperation that is going to be  
21 required between various sponsors, for ultimately, the  
22 maximal virologic effect for licensing trials with these  
23 agents is almost certainly going to be dependent upon their  
24 use in combinations.

1           We are going to have to have even more cooperation  
2 than we have had, and we have had a good bit. This is going  
3 to have to increase because other than getting your short-  
4 term Phase I data, I think most sponsors already are moving  
5 to use their drugs in combinations, which is quite  
6 appropriate, because that is the way you have to treat  
7 patients. However, I view that as something that is going  
8 to require a lot of work from all, from the Agency, from the  
9 sponsors, and from academia, is getting this cooperation  
10 even greater than it now is.

11           For licensing trials, I think we should have as  
12 our goal, suppression of viral replication for under 50  
13 copies for as long as possible for those people who are  
14 being treated.

15           Having said that, I think that I also would be  
16 comfortable in somebody with established disease whose  
17 cruising along on no therapy with 1- or 2,000 copies, to  
18 follow that person for a short period of time, maybe even  
19 for a longer period of time, but following them closely  
20 without therapy.

21           That level of replication, as best we understand  
22 it, is not going to immediately throw their immune system  
23 into a catastrophe, but if somebody is being treated, then,  
24 I think we have to have an actual suppression as our goal to

1 avoid selecting for a resistance and avoid making these  
2 drugs not useful for the patient.

3           Now, while complete suppression for as long as  
4 possible should be our goal, it is very clear that very  
5 often quite useful drugs, even when used in combination, or  
6 at least in some combinations, may not reach that goal, and  
7 I think that is fine, too. I don't think that we should  
8 demand that for licensing certainly, but that should be what  
9 we are working toward, and those drugs obviously in those  
10 combinations will prove to be of the greatest benefit to  
11 patients.

12           Now, I am less enchanted than some of my  
13 colleagues with the rate of fall in viral load because I  
14 think that (a) it is difficult to measure, and I would  
15 remind folks that 0.5 to 0.7 logs decline in RNA can be  
16 achieved with AZT alone with a nadir at about 7 to 12 days,  
17 but yet I don't think that any of us recommend that as  
18 clinical optimal therapy.

19           That is not to say that AZT isn't a useful drug,  
20 but we are going again to face the problem of using these  
21 drugs in combination, so I am simply saying that half a log  
22 means that you have got a real winner is not necessarily the  
23 case, but when used in combination you may, so again we are  
24 back to the need to gather data, and the difficulty in

1 gathering data about individual agents and there being used  
2 in combination, and this to me is the greatest intellectual  
3 struggle that I go through in trying to design trials.  
4 There are various add-on strategies or switching strategies,  
5 but this requires some additional work in another workshop  
6 probably on clinical trial design.

7           The durability is clearly critical, and it is for  
8 that reason that I favor looking for clinical trial purposes  
9 at a sensitive an assay as possible, because that does, as  
10 we have seen, very dramatically, today, correlate with  
11 durability of effects.

12           This makes some sense at least by our current  
13 understanding of the disease, that is, replication is  
14 necessary for the selection of the resistant mutants which  
15 account for a majority of the failures.

16           That is not to say, however, that even some  
17 patient who has replicating virus down below 20 copies might  
18 not ultimately break through, because there is a lot of  
19 virus onboard, but clearly, the durability of the effect is  
20 enhanced by achieving maximal suppression, whatever that is.

21           One group intrigues me, as indicated by some of my  
22 earlier questions, and that is the individuals who somehow  
23 do fall on treatment, and have their fall to below the limit  
24 of detection and then rise up to 1,000 or 2,000 copies, or

1 those folks who fall and then level off there.

2           These people are trying to tell us something. I  
3 am just right now not quite smart enough to figure out what  
4 they are telling us. Perhaps what they are telling us is  
5 that this virus, and a few anecdotal measurements suggested  
6 that this virus is wild type virus, not resistant virus. If  
7 it were a resistant virus, you would expect that it would  
8 rush forth considerably, to considerably higher levels  
9 unless it were very much compromised in its ability to  
10 replicate, so it could well be that this virus represents an  
11 emerging pool from provirus, which is wild type, which would  
12 be restrained, but not eliminated perhaps because some  
13 stimulus is making it come forth.

14           We need to study this group of patients really is  
15 what I am saying a lot more, so that I don't have to  
16 speculate, but so that I can speak from data.

17           What groups of patients should be studied? I  
18 think all of them, children, highly experienced people, and  
19 we need to know the effect of baseline status, and we have  
20 seen a lot of data on that in the analyses over the last two  
21 days.

22           You really must give your drug and your drug  
23 combinations an actual challenge. Licensing drugs in  
24 patients who have, to begin with, 1,000 copies, I am afraid

1 is not going to tell us what we need to know, so that while  
2 you need to get that information from the practical point of  
3 view of knowing what the drugs do in that group of patients,  
4 you must challenge them with patients who are more advanced  
5 in their disease and patients who are very much  
6 antiretroviral experienced, and there are large numbers of  
7 them around, and those of us who see patients are aware that  
8 they provide you with some of your thorniest challenges as  
9 to what to do.

10 I would also add, in addition to studying these  
11 three groups of patients, that all sponsors should  
12 incorporate into their trials designs, designs that would  
13 result in improved dosing schedules, something that really  
14 hasn't been mentioned very much the last two days.

15 Clearly, if you can take medications once or twice  
16 a day, that you are going to be much more adherent to the  
17 regimen, and the regimen will be much more successful if you  
18 are more adherent to it, because certainly in everybody's  
19 experience, some of the failures result from people not  
20 being as adherent as they should be to the demanding  
21 regimens.

22 So, if sponsors can incorporate into their trial  
23 designs and develop drugs, that sometimes known drugs that  
24 can be given less frequently, this would be a major goal,

1 and I am sure that the Agency would support such innovations  
2 in dosing.

3           The durability we can discuss a little bit more in  
4 the second questions.

5           DR. HAMMER: Thank you.

6           Just a couple of comments. With respect to the  
7 meaningful virologic response, I concur with my colleagues  
8 that no single definition applies, but also inherent in this  
9 question is what the Agency has put forward as the potential  
10 endpoint in the trial, and that is time to failure, which is  
11 an interesting concept, and just to go on record, I think  
12 for the reasons that have been stated by the Agency, it is  
13 quite a reasonable endpoint because of the subject retention  
14 that would be inherent in that, also, that it subsumes  
15 whatever definition of virologic response one puts in,  
16 particularly the maximal response.

17           So, just to go on record--and others may want to  
18 comment--I think the issue of a time to failure endpoint is  
19 interesting, although then it has to be defined as to what  
20 the success definition is, and then therefore what the  
21 failure definition is, but for the reasons stated, it is an  
22 intriguing way to construct an endpoint to a trial.

23           I think that the range of virologic responses is  
24 as stated. Personally, who you go after, and we should be

1 going after the maximum attainable virologic response, which  
2 should be proportion below the limit of detection with I  
3 think shut down in RNA and the lymphoid tissue.

4           Now, we are not going to be doing large Phase III  
5 trials biopsying lymph nodes in everyone, but we will be  
6 doing enough Phase II trials that we will be able to develop  
7 I think, at least for certain drug classes, the correlation  
8 of the level of sensitivity of the assay and the plasma with  
9 what that is doing to HIV RNA expression in the lymph nodes,  
10 as well, and ultimately, perhaps what happens to the  
11 proviral DNA pool.

12           Just as aside as to what level of sensitivity one  
13 wants to look at, I think it is a little premature today to  
14 say we should go for the under 50 assay. There is a lot of  
15 validation going on about those assays, as was discussed  
16 yesterday, and we really don't know how they perform, let  
17 alone how they will perform out in laboratories across the  
18 country.

19           So, as of today, I think we should be dealing with  
20 the assays that are validated under 4- to 500 copies, but  
21 rapidly we will be moving toward the 20 to 50 copy range. I  
22 also think it is a bit of a moot point because I don't know  
23 of any clinical trial that is going on now where  
24 pharmaceutical sponsors are not--and the ACTG, as well--not

1 looking at the ultra-sensitive assay as a co-primary  
2 virologic assay along with the standard assay, so this I  
3 think will take care of itself.

4           Also, I think this raises an issue from the data  
5 we have seen about drug class specific responses and how  
6 stable those responses are. For example, as was alluded to,  
7 with the Merck data, if you are under 500 in the 035 trial,  
8 there is a high proportion of those subjects who are also  
9 under 50, whereas, in the INCUS trial with nevirapine, you  
10 really had to be under 20 by what was reported to really  
11 feel stable in that durability of response and the depth of  
12 that response, so we can't lose sight of drug class  
13 specificity and the potency of regimens.

14           Also, as an aside, I think it was raised yesterday  
15 briefly, perhaps in the public comment session, I think the  
16 RNA kits, as they are developed, we only have one approved  
17 RNA kit of the standard assay, the Roche kit, we need to  
18 have these developed, approved, and validated, and kit  
19 labels should also be modified where the data support it to  
20 reflect how we use them in clinical practice. That, I think  
21 should push the kit manufacturers, as well as the  
22 pharmaceutical sponsors, to do the studies that are  
23 necessary to get that indication in the packaging of the  
24 kits.

1           So, moving from the maximum response, I think  
2 there is a range that is down to a minimum response. I  
3 think what the data show, as was stated by several of my  
4 colleagues, that you need at least a half a log reduction  
5 for X period of time, whether that is 16 or 24 weeks or  
6 beyond, to translate into a meaningful clinical response,  
7 however that is by no means an optimal target right now, and  
8 that would be really a minimally acceptable target, and not  
9 any one that I would suggest should be striven for by any  
10 regimen or any particular drug or combination.

11           What that means is that you can look for a  
12 proportion below the limit of detection, on the one hand,  
13 you can look at an absolute decline from baseline, on the  
14 other, and this relates to I think the baseline RNA that you  
15 started with in the subpopulation.

16           I think this can be easily handled in clinical  
17 trials with again co-primary endpoints or a primary and a  
18 secondary virologic endpoint, so to spend too much time on  
19 the semantics I think is not appropriate.

20           As far as the subpopulations that are listed, the  
21 question says should the definition differ for specific  
22 subpopulations. Personally, I don't think the definitions  
23 should differ because if you have a flexible definition or a  
24 definition that can be applied to different populations, it

1 will encompass that, but also I think we shouldn't, although  
2 it may be more difficult to attain maximum virologic success  
3 in these populations, it should still be what we are  
4 striving for, so I think the definition should remain the  
5 same, but our expectations need to be realistic at least  
6 with the drugs we currently have, but I don't think we  
7 should say and rest happily that it may be more difficult in  
8 children or naive or experienced individuals to achieve a  
9 substantial proportion below the limit of detection and  
10 therefore be satisfied if we don't do it. You need to  
11 strive for it and just be able to have clinical trials that  
12 allow you to analyze the data appropriately.

13           We should also remember that the Merck 035 study  
14 was AZT experienced individuals. It is a trial that has  
15 driven our thoughts about triple therapy, and achieved a  
16 remarkable proportion of success although the denominator is  
17 small in a triple therapy arm of 31 subjects. That was an  
18 AZT experienced population. So, you can achieve a success  
19 in experienced subjects.

20           Now, that AZT experience and protease experience  
21 are two different species to treat currently with our  
22 armamentarium as far as our ability to succeed and knowing  
23 what we are doing with alternative drugs, but what I think  
24 that means is that with better drugs and more drugs, the

1 challenge to treat successfully experienced subjects or  
2 patients with more advanced disease or children with higher  
3 viral loads should be there, and I don't think we should  
4 change our definitions.

5 I would also suggest that as the regulations or  
6 the requirements or label indications change, that perhaps  
7 the Agency can require either studies that encompass the two  
8 different populations or three different populations or two  
9 different studies.

10 One fully expects that pharmaceutical sponsors  
11 will want to study a population that will show off the drug  
12 or particular combination to its best light in naive  
13 subjects, and I don't think that should be discouraged  
14 because, in fact, we have learned some very interesting  
15 things.

16 Remember, it took us several years with nevirapine  
17 development to finally find a population where people could  
18 feel very comfortable with what that drug was doing in  
19 combination, and all the experienced trials beforehand there  
20 was a lot of pessimism, but the INCUS trial at the eleventh  
21 hour essentially turned around the thoughts about that class  
22 of drugs, so naive populations are important to study, but I  
23 think also should be required the more challenging groups of  
24 patients that have been stated, and in particular, I think

1 the greatest need besides children are the experienced  
2 subjects, particularly patients who cannot tolerate or are  
3 failing protease inhibitors. That is a substantial  
4 proportion of the population in this country in all of our  
5 outpatients departments.

6           Just briefly because I think they do run together,  
7 Part C is what would constitute a loss of that response. I  
8 think it depends on your definition of virologic success, so  
9 if you are going for the maximum of below the limit of  
10 detection by whatever assay, failure is a confirmed rise  
11 about that, and if it is 400 or 500, or 20 or 50, I think  
12 that is logical to think about it.

13           You need to have the assay variability and the  
14 assay characteristics in that definition. You need enough  
15 confirmatory samples to be sure it is not variability, that  
16 it is not biologic variation, that it is not an intercurrent  
17 illness, and that is not a vaccination, but that is  
18 ultimately where we are going, and again, I would just  
19 reiterate that what we are going to want to see in plasma  
20 assays is what reflects in the lymphoid tissue and  
21 potentially other reservoirs.

22           If you are going for an absolute change from  
23 baseline in populations that you cannot achieve the  
24 demarcation of below the limit of detection, then, it is

1 going to be some loss of response depending upon what the  
2 maximum response is, but at the limit at least, returning to  
3 within a half a log of your original baseline is certainly  
4 going to be a loss of response, and probably that is going  
5 to be a little too late.

6           As far as just the followup, how long should the  
7 responders be followed to assess durable virologic response,  
8 again, that is an open-ended question, one that is  
9 difficult. From the data we have seen, we have precious few  
10 data on patients followed 48 to 96 weeks and beyond, very  
11 few patients.

12           I think any trial that is looking for durable  
13 virologic response as an indication, the absolute minimum is  
14 going to have to be 48 weeks, and I would suggest that it  
15 should be longer than that, and perhaps studies with enough  
16 flexibility in them to look at patients 48 weeks after the  
17 last subject is enrolled will give you an average followup  
18 depending upon your enrollment accrual period of 66, 72, and  
19 et cetera, weeks as far as an average length of followup,  
20 that begins to put together a reasonable package for  
21 durability at least in my mind, but 48 weeks would be the  
22 absolute minimum, and I think that is a little bit  
23 borderline, particularly if we are going to make accelerated  
24 approval decisions based on 16 to 24 week data.

1           Before moving on to Question 3, there are some  
2 panelists who chose to separate Questions 2 and its various  
3 parts, and I would just say is there anyone that wants to  
4 add comments to Parts 2C and 2D or add any other comments on  
5 Question 2. Mark.

6           MR. HARRINGTON: One of my concerns is that  
7 protocol development may be too rigid and that that may make  
8 it difficult to interpret trials, and the new standard of  
9 care is really based on giving a person with HIV and their  
10 physician options and thoughts and reflections about when to  
11 switch therapy, because it isn't at all clear when one  
12 should switch therapy.

13           There is people who coast along a little above, a  
14 little below the limit of detection. There is people like  
15 Fred was talking about who tootle along at 5,000 or 20,000.

16           If you look at the Mellors risk tables in the  
17 guidelines document, if you have under 14,000 RT PCR copies,  
18 your three-year risk of progression to AIDS in that study  
19 was zero, and under 41,000 RT PCR, your three-year risk of  
20 progression to AIDS was only 8 percent.

21           So, I think there is a difference between a  
22 virological switch point and sort of a clinical danger  
23 point, and I think that people need to be given options.  
24 They need to be given the option of switching and maybe

1 either being re-randomized or going off study drug at a  
2 certain point, and the different points include returning to  
3 detection in a reliable way, which would mean probably at  
4 least two measurements or it might depend on the magnitude  
5 of the rise. If it has gone up half a log, you may not be  
6 at much risk, if it has gone up 2 logs, or back to baseline,  
7 you clearly want to think about switching.

8           If you are still undetectable and there is a  
9 persistent CD4 drop or symptoms, again, I mean you have to  
10 go back to the guidelines. It is a multifactorial decision  
11 to switch, and you have to consider giving the person with  
12 HIV and the physician the freedom to switch and possibly be  
13 re-randomized to a follow-up study, but you don't want to  
14 put a straitjacket on what that is, so it really is  
15 multifactorial.

16           DR. HAMMER: Right, and some studies are having a  
17 stringent virologic failure definition, but not a mandatory  
18 switch at that point, an option for patients at the  
19 virologic failure point, to give that option, but then a  
20 mandatory or it is a suggested switch for higher viral loads  
21 that really show clear-cut failure, and that kind of  
22 flexibility at different levels which are confirmed is  
23 important within the trials.

24           DR. MURRAY: I would like to interject just to

1 clarify. I think we have kind of separated loss of  
2 virologic response and switch criteria, and that you might  
3 want more stringent criteria for what a loss of virologic  
4 response is for evaluating drug efficacy. That is why 2  
5 begins for the purpose of evaluating drug efficacy.

6 In Question 3, then, we talk about switch criteria  
7 and if that should be different than your endpoint, so if  
8 you could kind of take that into consideration when you are  
9 giving us a response.

10 DR. HAMMER: That is sort of what we were just  
11 discussing. In fact, I think we agree with you that the  
12 loss of virologic response does not have to necessarily  
13 mandate a switch, but you also have to have potentially that  
14 option.

15 MR. HARRINGTON: Yes, I think it is a nested group  
16 within the larger group of options that you would switch  
17 for, but I also think as far as how long should responders  
18 be followed, I think the great majority of people in the  
19 trial who were responders should be followed, so that we can  
20 go way beyond the median time to failure, because there  
21 might be a very long tale of failure that was seen in some  
22 of the AZT/3TC responders.

23 By 16 weeks, a lot of people had failed, but then  
24 there was not a lot of failure in the next 16 weeks among

1 the people who had made it out, so you would need to know  
2 what was going to happen to that second half, and then for  
3 safety, you would probably want to follow them until the  
4 great majority of people had failed.

5 MS. LEIN: In terms of what would constitute a  
6 loss of the response, as I had mentioned earlier, I really  
7 that response needs to be defined depending on the  
8 population that is being study, and this is when not having  
9 the information on those who did not respond is really  
10 harmful to guiding the FDA in instructing and assisting  
11 industry in designing studies, particularly because I think  
12 that those people who have failed all other options or who  
13 may be in more advanced stage disease, there should be a way  
14 to encourage industry to study these folks and to look at  
15 this population as a desirable population for drug  
16 development.

17 So whereas, in one instance, if the meaningful  
18 virologic response is a viral load below the limit of  
19 quantification, then, perhaps a loss of response may be  
20 multiple measures of HIV RNA of 0.5 logs above their nadir  
21 without other explained causes like vaccination, et cetera,  
22 or maybe 1 log on two times points or something.

23 But in terms of those people who the meaningful  
24 virologic response may be a 1 log reduction in HIV RNA, and

1 it is still quantifiable, but showing that it is an active  
2 drug, perhaps a loss of that response may be a return to  
3 baseline or even time to 0.5 log increase above baseline, is  
4 looking at the criteria and guiding industry around that  
5 group as something distinct.

6 DR. HAMMER: Any comments on 2C or 2D? Judith.

7 DR. FEINBERG: I think that the notion that the  
8 definition of loss of response would be the reciprocal of  
9 the definition of success makes great sense, and I agree  
10 with Scott that any definition within a specific trial  
11 should encompass, you know, in the terms of the definition,  
12 the assay variability component.

13 I guess I have a concern of what the mathematical  
14 definition of failure is given that, in fact, these viral  
15 load tests are continuous and that, as Dr. Dale pointed out,  
16 there are levels of virus below the limit of detection, so-  
17 called limit of detection that can actually be measured.

18 So, I am concerned the definitions of failure and  
19 success, since they are bound together, be thoughtful about  
20 whether we are talking about the arithmetic increase of a  
21 copy number above 400 for the RT PCR assay or whether we are  
22 really looking for something more or less substantive than  
23 that.

24 Just outside the context of clinical trials, I see

1 many patients who bounce around this detectable level, and  
2 yet who are clinically fine, and I am not sure what that  
3 means. Of course, I think everybody buys into the concept  
4 that no viral replication would be the best of all possible  
5 worlds, but, you know, even going to these more ultra-  
6 sensitive assay, people who do well still do, in fact, have  
7 some detectable virus.

8           So, I am a little anxious about how artificial  
9 that seems to me, that a patient with 399 copies is a  
10 virologic success and a patient with 401 copies is a  
11 virologic failure, and I don't know what the answer, but in  
12 my mind, this really requires some further thought.

13           First of all, in both the realm of drug  
14 development and the realm of clinical practice, there needs  
15 to be a way to assess a drug or drug combination is doing  
16 something and that it works and that is beneficial to the  
17 patient, but the flip side of that, of doing no harm, is not  
18 to prematurely decide that something doesn't work and isn't  
19 going to benefit a patient, and I think that already, within  
20 just a year of these drugs being on the market, the earliest  
21 protease inhibitors, it is really quite clear that there is  
22 shared class resistance.

23           I think if the mathematical definitions of failure  
24 and success are too artificially tight, I am concerned that

1 in both treatment and drug development realms, we sort of  
2 run through what is available far too soon, I am not sure  
3 that benefits either the pharmaceutical companies or the  
4 patients.

5 In terms of durable virologic response, as I said  
6 before, to me a response is both that the viral load does  
7 something and that it does something for some substantive  
8 period of time. You know, on some level, I don't see how  
9 you can separate them, and I would argue for the longest  
10 possible followup that could be done.

11 I would say at a minimum Scott's proposal of a  
12 year after the last patient is entered would then give you a  
13 median duration that would clearly be more than 48 weeks to  
14 begin with, but I think long term we need to know, because  
15 all these things are interconnected and bound up together,  
16 we need to know not only about durability, but that is going  
17 to say something for the patients who don't have a durable  
18 response.

19 There is clearly some implications then about  
20 resistance development and subsequent treatment paths or  
21 subsequent treatment strategies, not to mention the fact  
22 that when we approve drugs in a relatively limited data set  
23 of patients, there are always safety issues that surface  
24 later, and so the longer we have those folks in a very

1 supervised trial setting and can get that data in a  
2 systematic way, I think the better off we would be.

3           So, I again, I am also I guess with Scott who said  
4 that maybe this should be open-ended, but I would argue for  
5 in all situations, longer is better.

6           DR. HAMMER: Fred?

7           DR. VALENTINE: No, thank you.

8           DR. HAMMER: John.

9           DR. MODLIN: Just a quick footnote to Judith's  
10 last comment about durability of the virologic response, and  
11 this was reflected in a question I asked earlier.

12           I agree that there is no question that if you want  
13 to learn everything you should know about an antiviral  
14 regimen, it is important to follow these patients as long as  
15 you can for purposes of resistance, long-term outcome, et  
16 cetera, is critically important.

17           If, on the other hand, your sole purpose is to  
18 compare two regimens that you already feel you know as much  
19 about as you want to, it looks like from all the data we  
20 have seen so far that the differences between those regimens  
21 can be adequately distinguished by that six to 12 months of  
22 therapy.

23           DR. HAMMER: Wafaa.

24           DR. EL-SADR: Again addressing the issue of

1 switch, I hope we are not naively sort of thinking that if  
2 we decide to do virological endpoint studies, that whoever  
3 is randomized in whatever arm will stay in it until they  
4 reach a switch point or the end of the study.

5 I think we are going to have the same thing that  
6 happens now with clinical endpoint studies, is people will  
7 stop drug, people will switch to the other arm, and so on,  
8 and so we are always going to be in the same dilemma of  
9 having people go off the treatment arm that they are  
10 randomized to at a rather disorganized manner, which is real  
11 life in randomized trials.

12 The reason I am concerned with the virological  
13 endpoints is that it is almost going to be an on-treatment  
14 analysis, and the treatment is going to be having viral load  
15 assay. So we have to be careful what we are going to do  
16 about people who somehow do not come back for viral load  
17 measurements, are we going to consider them as failures or  
18 are we going to consider them as successes, and also, people  
19 who are going to go to other drugs for toxicities or some  
20 other reason, so I think we are going to have to decide in  
21 the analysis if we are going to a very lab-oriented  
22 endpoint, to also take into consideration how we are going  
23 to categorize missing data, people who have switched to the  
24 other treatment arm, and so on, well, of course, we have to

1 stick to the intent to treat.

2 DR. ELASHOFF: I think it is our intention we  
3 would count those people as endpoints, so that there would  
4 be no missing data. They would be treated as endpoints,  
5 just as if they had come in, had their RNA measurements, and  
6 RNA was found to be increasing.

7 DR. EL-SADR: So it would be like as if they had  
8 whatever we decide on.

9 DR. ELASHOFF: So if they drop out, it was  
10 presumed that they would be an RNA failure.

11 DR. HAMMER: Chris.

12 DR. MATHEWS: The definition of a loss of a  
13 virologic response raises a question I don't think we had  
14 had to face before because we were so heavily linking  
15 laboratory parameters and clinical events in the definition  
16 of failures before, but this whole discussion seems to lead  
17 one to the conclusion that you could have an individual or  
18 group of people who developed major clinical events, but  
19 maintained viral suppression, who would not be counted as  
20 failures of the therapy.

21 I don't know about the rest of you, but I have  
22 treated a number of patients in the last couple of years who  
23 have been hospitalized with major opportunistic events who  
24 had, on their last measurement, undetectable viral load.

1 They tend to be people who had very low CD4 counts, who had  
2 poor CD4 responses despite a robust viral load response.

3 DR. FLYER: What would your suggestion be on that,  
4 because we have been, on a preliminary basis, thinking if  
5 you see a clinical endpoint, that would count as a failure  
6 because our presumption is that if there is a clinical  
7 endpoint, treatment modification is most likely, do you have  
8 any thoughts on the best approach?

9 DR. MATHEWS: I mean I think you could argue  
10 either way. I think you could argue that there are other  
11 determinants of the clinical events, that there is all this  
12 information about the immune function of the lymphocytes.

13 DR. HAMMER: One possibility I think, as a  
14 secondary, obviously, clinical events would be accumulated  
15 in any primary virologic endpoint trial as one of the  
16 secondary objectives would be to catalog major clinical  
17 events along the way.

18 One could also think about, as a secondary  
19 objective, the cataloging of a combined virologic failure, a  
20 clinical failure, or a CD4 end failure. I mean we have done  
21 aggregate endpoints with CD4 before, a 50 percent decline in  
22 CD4 cells, which had their problems because they were driven  
23 by the marker. This may or may not be driven by the marker,  
24 it largely would be, but one could think about some analysis

1 as a secondary analysis that is planned, that takes into  
2 account a failure based, not just on the individual  
3 virology, CD4, and clinical, and then combines them into  
4 some analysis where you can get a combined look.

5 I don't know how else you can do it.

6 DR. MATHEWS: But are you proposing that the  
7 primary endpoint be based simply on time to virologic  
8 failure?

9 DR. HAMMER: I think if the trial is being  
10 designed for a label indication for durable RNA suppression,  
11 I see the primary endpoint and objective of that trial being  
12 virologic, and it won't be powered for clinical events, so  
13 the clinical failures will have to be obviously very  
14 carefully looked at even if the numbers are small, but the  
15 only way they could be analyzed is in some secondary  
16 fashion. It would give me great pause if the numbers were  
17 discordant with the virologic success.

18 DR. FLYER: Well, we have been thinking about as  
19 we get full packages, which will hopefully have people with  
20 active disease, that we will see enough endpoints that we  
21 could get confidence intervals on the difference between the  
22 treatment, so that we could see if we could rule out  
23 meaningful differences, so we were thinking of it maybe a  
24 little bit higher than secondary, whatever that is, so that

1 would be a major analysis to rule out important differences.

2 DR. HAMMER: There is another caveat there. If  
3 you want enroll patients with very advanced disease or  
4 borderline active disease, the flurry of cases of early  
5 presentations of MAI and CNV and pneumocystis that one sees  
6 in the first few weeks after potent therapy, so it adds yet  
7 another complication to the interpretation of a  
8 histologically or microbiologically document opportunistic  
9 infection.

10 So, even if you prove it, it doesn't necessarily  
11 help your analysis in this sense. You really have to look  
12 at the data primarily and secondarily. I am no sure we will  
13 solve this today, but Chris' point is very well taken that  
14 you can't--and I think it gets back to oversimplifying RNA  
15 as the only thing you look at with blindfolds on.

16 No one I think is suggesting that, but it needs to  
17 be stated that there may be major issues that come up with a  
18 particular drug or drug class or combination that give you  
19 major pause clinically, that look great virologically.

20 Fred, did you have some comment on 2C or 2D?

21 DR. VALENTINE: Yes. Addressing 2C, the loss of  
22 response, I think that, practically speaking, you are going  
23 to have people leaving a trial if they go up 1 log on  
24 repeated measurements, and I think that is a reasonable

1 group, a reasonable cutoff to consider a response and a  
2 practical one.

3 We still have to deal with the group of people who  
4 might have a profound drop and then hover there at a lower  
5 level with this "new" setpoint, whatever that concept is,  
6 and I am not sure that I would necessarily call them  
7 failures.

8 However, having said that, I think the most  
9 important aspect of Question 2C is we must determine the  
10 reasons for failure, and clearly, any sponsor is going to  
11 want to know whether the failures result from failure to  
12 adhere to the regimen, whether the failure is a result from  
13 the development of resistance, or whether the failure is  
14 really a result from wild type virus persisting, a sort of a  
15 failure of pharmacological action, and that may be due to  
16 the concomitant administration of other drugs that are  
17 interfering with the antiretroviral agent or as of yet  
18 unknown factors, but the real question in failures is why,  
19 why are they occurring.

20 The durability, how long should they be followed,  
21 well, obviously, I think that the patients would like to be  
22 followed forever, and all sponsors would like to know how  
23 many years their particular regimen is effective.

24 That would not obviously be necessary for

1 approval, and there I think your criteria of a year after  
2 the last person comes on the trial is certainly a reasonable  
3 one, but we really want to know how long it will go for  
4 very, very long periods of time.

5           The issue that Chris just raised about clinical  
6 failures with low viral loads is a very real one, and  
7 relates to the discordance that we saw in those two quadrant  
8 plots yesterday of patients who might respond with low viral  
9 loads, but not respond with CD4s, so those people are also  
10 very worrisome.

11           As far as approval, if you had either clinical  
12 failures or CD4 failures, which we have seen are an  
13 independent predictor of clinical outcome in all of the  
14 analyses we have heard over the last two days, I would think  
15 that they would have to be taken into consideration as a  
16 criteria for the study for approval, and that if things  
17 don't fit together in a substantial portion of patients,  
18 then, there is a puzzle here and that RNA by itself may not  
19 be sufficient, even though I will admit that if the label is  
20 the drug is for the treatment of RNA, that it is hard to  
21 argue that, but that the implications of approving a drug  
22 for the treatment of RNA, when really most patients are  
23 concerned about being treated as patients and being treated  
24 clinically, might warrant adding these additional caveats of

1 clinical endpoints which would be very acceptable, but even  
2 of CD4 or some other immunologic measurement should we ever  
3 discover something that is a little bit better than CD4.

4 DR. HAMMER: Another reason to overpower these  
5 trials virologically, so that you would gather as much  
6 clinical information as you can.

7 DR. VALENTINE: Good point, yes.

8 DR. HAMMER: For the audience's sake, I have just  
9 been apprised that the air conditioning has just been  
10 repaired, so I think on that note we can move on.

11 There is one more question. We have tackled the  
12 major central question, which was No. 2. The third question  
13 has two parts.

14 A. What events should prompt altering randomized  
15 therapy during a clinical war? We have begun to slip into  
16 that discussion.

17 B. Are there circumstances in which this would  
18 differ from the virologic endpoint?

19 Maybe I will start on my left. Fred, do you want  
20 to start this discussion?

21 DR. VALENTINE: I think the basic trial design  
22 proposed by the Agency is a rather attractive one if we are  
23 going to go for suppression, then, the duration to endpoint,  
24 which would be recovery by the criteria we have sort of

1 danced around here would be reasonable.

2 I should point out for some of the questions  
3 raised by our statisticians that there are trials now in  
4 which suppression has been achieved in 80 percent of people  
5 for well over a year below the level of detection, even at  
6 the 50 copy level.

7 We just don't have a lot of data on longer  
8 followup, but this is a feasible concept for that duration.  
9 Most of the data we saw did not deal with those studies, but  
10 that has been achieved in moderately advanced patients in at  
11 least one study. So this is something to shoot for.

12 Then, the duration to failure would be a very  
13 acceptable endpoint if you get there, if you get below the  
14 level of detection to begin with, again, with the caveat of  
15 this interesting group of people who level off at another  
16 level.

17 What events would be altered? Altering  
18 randomization would clearly, as indicated by the proposed  
19 trial design, there would be a switch with a rise with  
20 predetermined level in RNA copy number or with the issues  
21 raised, what would you do with the clinical event, what  
22 would you do with the dissociation between CD4 and RNA.

23 That is a tougher one. We are going to have to  
24 think very hard about that because you are changing a drug

1 that affects virus, not those other endpoints, and I don't  
2 know to deal with that unless, as somebody said, although  
3 there is no evidence for it, that the drugs themselves are  
4 inhibiting the lymphocyte function, but I don't know of any  
5 evidence for that, if anything, they seem to help function,  
6 although I would say that those of you who follow the  
7 abstracts in this area, and a couple of papers would note  
8 the immunologic improvement, improvement does occur as  
9 evidenced by what happens to patients, they do better, and  
10 as what happens, evidenced by what happens to some of the  
11 immunologic measurements, that no one yet really has defined  
12 full immunologic reconstitution even with prolonged  
13 suppression of HIV, that is, not only do CD4 cells come back  
14 up to normal, but some of the analyses of T cell repertoire  
15 indicate gaps still remain and function does not return to  
16 all what we call microbial antigens, and there is very  
17 minimal return at least as of yet described of regain even  
18 or even initiation of immune response to HIV itself.

19 My own private definition of immunologic cure  
20 would be when this viral disease is treated by the immune  
21 system like any other viral disease, that is, when the  
22 immune system finally and belatedly starts to mount  
23 effective immune responses against HIV itself, and we just  
24 haven't seen that.

1           That is asking a lot of an anti-HIV agent, that  
2 is, to correct the situation sufficiently, so that the  
3 immune response responds to HIV itself, but you can always  
4 hang that out in front of you if you think you know  
5 something is a long term goal to keep you motivated, so we  
6 are not there yet.

7           Circumstances in which this would differ from the  
8 virologic endpoint, well, I think they have already been  
9 mentioned. You certainly want to change your therapy or to  
10 stop and reconsider where you are if you had serious  
11 clinical endpoints or if the immune system continued to  
12 crash in spite of having a sustained suppression. Those too  
13 would make me want to call it an endpoint, and a change even  
14 though it would be different from the primary endpoint of  
15 time to return of virus.

16           DR. HAMMER: Pamela.

17           DR. DIAZ: Well, I think anything that I would say  
18 regarding this particular question has already been said. I  
19 am not sure I know the complete answer to this, but  
20 certainly other than virologic endpoints, clinical events  
21 will have to be looked at very carefully and likewise  
22 immunologic status.

23           DR. HAMMER: Chris.

24           DR. MATHEWS: I mentioned this earlier and I would

1 reiterate it because I think it is very important that the  
2 analysis of the data sets that have been presented for the  
3 last couple of days should be continued to look at the one-  
4 month response of this issue of the concordance between the  
5 practice guidelines that have been recommended and what, if  
6 any, are put into place for clinical trials are as  
7 concordant as possible.

8           It is a very simple analysis with an ROC curve.  
9 Should it be a half a log drop, 0.75 log? Maybe it would be  
10 six weeks instead of four weeks, but this data would be very  
11 profitably analyzed for that purpose.

12           I think the other points have been made on that.

13           DR. HAMMER: Judith.

14           DR. FEINBERG: I won't reiterate the other points  
15 where I agree with my colleagues. I just, in addition to  
16 that, want to sound once again a cautionary note that the  
17 switch point or the criteria that would define what happens  
18 to the viral load, that would then trigger a switch, in my  
19 mind, it needs to be set conservatively enough, so that the  
20 individuals who are going to eventually achieve a virologic  
21 response are given adequate time to do that.

22           I don't see that it benefits either drug  
23 development or patient care for us to be giving people drugs  
24 for a week or four weeks or six weeks or eight weeks at a

1 clip, and then decide in their 401 copies and that they  
2 should go get some different set of drugs.

3           There are, in fact, in reality not that many  
4 choices. So, you know, that is my biggest concern, and I  
5 agree with my colleagues about the other issues, so that is  
6 my biggest concern, about prompting a switch to therapy.

7           You know, everyone always talks about, well, the  
8 pressure from the patients, the pressure from the community,  
9 and I think that, in part, our responsibility is as both  
10 investigators and as regulators and as drug developers,  
11 speaking on behalf of the pharmaceutical companies, would be  
12 to educate people with HIV infection that it might not  
13 conceivably be, we don't know yet, whether it is in people's  
14 best interest to switch drugs after they have 410 copies,  
15 because the functional reality is, is you just don't have  
16 very far to go with folks.

17           DR. HAMMER: Thank you.

18           Jim.

19           DR. LIPSKY: Fred's comments in bringing up a  
20 couple of issues which some of the members of the public  
21 mentioned, and I think should be mentioned, and one thing  
22 that has almost gotten lost here, it has almost been a given  
23 that we understand the pharmacokinetics and the  
24 pharmacodynamics of the antiviral therapy, and as mentioned,

1 I think that it is going to be difficult because to  
2 understand this clearly, we may need monotherapy in some  
3 patients for a period for time and as we develop a better  
4 understanding of what is happening with resistance, fall in  
5 virus, et cetera, that may or may not be appropriate.

6 We don't know, for instance, do you need to  
7 maintain a certain viral level constantly, do you need to  
8 treat every day, et cetera. The evidence seems to be yes,  
9 yes, but that may not be so for all agents.

10 The mere fact that T cells will improve is good,  
11 but may not be completely appropriate, as I think Fred was  
12 alluding to, and there was some mention in last week's  
13 Science, amongst many other places, that sometimes the cells  
14 that come back can be good, and sometimes they are not all  
15 that was before.

16 There was public comment about they would hope  
17 that the focus on viral markers would not preclude looking  
18 at other immunologic therapy of this disease, and I think  
19 certainly that this would not occur, because I think we know  
20 that the whole story may not be in just keeping the virus at  
21 the absolute lowest amount, although this may be an absolute  
22 necessity, but it may not be the whole story.

23 The question is what events should prompt altering  
24 randomized therapy during a clinical trial. One thing that

1 comes to mind is how do you--and something that has been  
2 brought up--what does a glimmer of hope of something that is  
3 a heck of a lot better than what a patient is on now, when  
4 does that prompt an alteration.

5 I think that we are developing a lot better  
6 understanding of response of agents in the disease and maybe  
7 some of the problems with some of the clinical trials is  
8 that they were developed when there were official--you know,  
9 promulgating exactly how you should treat something is  
10 always dangerous when we don't really know that clearly, and  
11 there are promulgations in Europe and others with two  
12 therapies, et cetera, and trials were developed during that  
13 time, but an issue comes up and maybe there should be  
14 clearer guidelines on when is it felt that there is  
15 something better out there and current trials should stop.

16 DR. HAMMER: Thank you.

17 Wafaa.

18 DR. EL-SADR: I think the key to enrolling  
19 clinical trials and completing and retention of participants  
20 is really that the trials have to reflect good clinical  
21 practice, what is accepted as good clinical practice, and be  
22 in conjunction with what knowledgeable clinicians and  
23 knowledgeable patients want for themselves or for their  
24 patients.

1           So, I think we have to be careful in the design of  
2 the studies and the switching and the requirements for  
3 getting off the trial, that we as much as possible are  
4 reflecting what is accepted as good clinical practice, and I  
5 realize there are some problems with the proposed guidelines  
6 that are in the public comment arena at this point, and  
7 their suggestions versus what the data we saw today and  
8 yesterday, and I think we need to respond to that because  
9 that is going to have a major impact on the conduct of these  
10 trials and getting the answers.

11           So, in a way I think we need to as much as  
12 possible be in sync with what guidelines are saying and also  
13 be realistic, to do or to allow within the trials what  
14 really clinicians would want to do, and I think for a  
15 clinical event, they would want to take that patient off  
16 that arm or switch them or whatever, as well as for maybe  
17 immunologic deterioration, maybe for other reasons, as well,  
18 but I see that it is critical that from the FDA perspective,  
19 from the sponsor's perspective, as well as from the  
20 guideline development perspective, that people come  
21 together.

22           DR. HAMMER: Vernon.

23           DR. CHINCHILLI: I don't have anything.

24           DR. HAMMER: Joel, do you have anything?

1 DR. VERTER: No, it has basically been said.

2 DR. HAMMER: John.

3 DR. MODLIN: Just a quick comment. I want to  
4 remind everyone that in the original randomized trial of  
5 intravenous AZT, which was conducted in very sick patients  
6 who had already had a history of having had pneumocystis,  
7 that it took about six to eight weeks before there was any  
8 diversions whatsoever between the treatment arm and the  
9 placebo arm in terms of clinical events, which of course  
10 were either death or development of a new opportunistic  
11 infection.

12 It is a group of patients with very advanced  
13 disease, and they are being treated with a drug AZT, which  
14 we now recognize as not nearly as potent as our current  
15 antiviral therapy, but the point I want to make is, is that  
16 events continued to happen to these patients despite the  
17 fact that there ultimately was some clinical benefit  
18 demonstrated, but it took six or eight weeks for that to  
19 occur.

20 So, in terms of events that prompt any change in  
21 therapy, either from a protocol standpoint or perhaps more  
22 importantly from a clinical standpoint, I think it might be  
23 unwise to make changes very early in the course of  
24 enrollment on a new protocol.

1 I would have to ask Fred, obviously, there is some  
2 delay between whatever immunologic reconstitution is going  
3 to occur, is going to occur, it is going to take some time.  
4 That may be the reason why that phenomenon is seen, but it  
5 may be wise not to make major changes in the first few weeks  
6 after starting on a trial compared to later on.

7 I don't know whether this needs to be built into  
8 the protocols or not. I would be interested in what other  
9 people have to say about it, but it is appropriate to what  
10 we have just been discussing.

11 DR. HAMMER: John, with regard to 3A and altering  
12 treatment in a randomized trial, is there anything specific  
13 to the pediatric population that is worth mentioning, growth  
14 rates, or whatever?

15 MR. MODLIN: Again, I think I have already  
16 mentioned and others have mentioned that we just don't have  
17 enough data yet to be very specific about what the exact  
18 appropriate virologic endpoints may be for a pediatric  
19 child. They may be the same as we have been discussing for  
20 adults. It may very well be that they will be somewhat  
21 different, that necessarily will have to be different based  
22 on the experience with the current highly active  
23 antiretroviral therapy that is going on in children now, so  
24 I think it is very difficult to be much more specific about

1 Question 3 until we have that information.

2 DR. HAMMER: Thank you.

3 Brenda.

4 MS. LEIN: I kind of agree with what Wafaa said,  
5 and if I heard you right, it was that clinical trials should  
6 allow for standard of care to be practiced and therapies  
7 switched, and trials should be designed to enable getting  
8 that loss of response or that virologic endpoint and still  
9 encompass some suggested standard of care guidelines,  
10 perhaps additionally, with additional guidelines regarding  
11 switching depending on the individual therapies being  
12 studied and their particular adverse events.

13 So I see lots of circumstances that the decision  
14 to alter randomized therapy would differ from the virologic  
15 endpoint. As we are talking about it, so many specific  
16 instances have come up in my head of, you know, patients  
17 that we work with at Project Inform who have gone on  
18 aggressive therapy, seen great decreases in viral load to  
19 below the limit of quantification, and yet seen progressive  
20 declining CD4 counts, an explosion of things like KS and  
21 other events, all of which wouldn't be virologic endpoints,  
22 but maybe reasons to change therapy, and so I think that  
23 there needs to be a lot of room in terms of the  
24 circumstances that would prompt altering therapy, but also

1 specific guidance.

2 DR. HAMMER: Mark.

3 MR. HARRINGTON: Yes, there are effects of these  
4 drugs that may affect other parameters besides the virus  
5 that may be very relevant and that we may be learning things  
6 about. For example, there is a whole spectrum of GI-  
7 associated disorders with the protease inhibitors, and we  
8 have recently found out about diabetes.

9 We don't really know all about this spectrum. We  
10 don't even know if it is captured by the way we do toxicity  
11 in trials, so there is a lot of things that are going to  
12 subjectively affect a person's willingness to continue, and  
13 we want to figure out how to capture that to guide  
14 management, so there is a number of things that are not  
15 viral load driven that are going to be relevant.

16 On the other hand, I want to go back to clinical  
17 endpoints. I think there is a little giddiness here that we  
18 are going to somehow not have any more, if we just don't do  
19 trials with any clinical endpoints, and tragically, that is  
20 not the case, and there are still going to be, and it is  
21 still very important to learn what happens to people even if  
22 we are giving them the best possible therapy, and there are  
23 circumstances where switching them for an OI is not  
24 necessarily--it may be good as a choice, but it may not be

1 the wisest thing for them to do, and as John said, it may be  
2 the first few weeks after they start in the trial.

3           It may be opportunistic infections in patients  
4 with holes in their immune repertoire, like Mark Jacobson  
5 has reported on with CMV. Countries are increasingly doing  
6 multinational studies where there are different standards of  
7 care in different countries, and there will be opportunistic  
8 infections in some of the countries like possibly in the 22-  
9 country recent first-line study that was done.

10           Also, we need to know about differences in  
11 incidents of opportunistic infections in trials where  
12 certain agents may be active against more than one virus,  
13 like 3TC is active against hepatitis, and adefovir is active  
14 against a number of other herpes viruses.

15           That is going to tell us very important  
16 information about how to optimize the use of the drugs, and  
17 so I think the FDA needs to look at composite event rates  
18 for viral load driven changes, toxicity driven changes, CD4,  
19 and the clinical events which will inevitably occur until we  
20 can figure out a way to truly reverse the immune  
21 suppression.

22           DR. HAMMER: Thank you.

23           I think in summarizing there has been consensus to  
24 3A that certainly there will be other events that will

1 prompt changes in therapy, clinical events which have to be  
2 looked at very carefully for when they are occurring and  
3 what they mean, CD4 progressive declines in toxicity or in  
4 tolerance.

5           The virologic failure thing, I would just mention  
6 one thing. If you define in a trial what virologic failure  
7 is, and to do it stringently, you are in a conundrum there  
8 in the sense that you may not operate clinically to switch  
9 therapy, but you also have to potentially offer the patient  
10 the choice at that point. Even if you set another higher  
11 threshold for where you would mandate or think that it is  
12 appropriate to come off treatment or switch treatment, you  
13 can't tell a patient or a physician that you have  
14 virologically failed by our strict definition, but you can't  
15 switch.

16           I think the option has to be there with obvious  
17 education that maybe it is not the appropriate time to do it  
18 if there are no other options. On the other hand, it is  
19 possible to nest additional studies within such  
20 circumstances, and the issue of this great increasing  
21 interest in intensification, both in people who are already  
22 suppressed, and prolonging that success, but also in people  
23 that fail at low copy numbers, if they meet a virologic  
24 definition, is that a time where an additional therapy in

1 fact could save or prolong the therapy that is being  
2 administered if substantial resistance has not occurred, and  
3 we have seen some results in that regarding the  
4 ritonavir/saquinavir study.

5           So, in fact, there are ways to use a stringent  
6 definition, a way to study other aspects down the line of  
7 prolonging benefit. As far as B is concerned, I think it is  
8 unanimous, are there circumstances in which changing would  
9 differ from the virologic endpoint, I think the simple  
10 answer is yes, and I won't say more about that.

11           That concludes the discussion points the panel has  
12 been given. Are there additional items you wish us to  
13 consider? For one of the few times, we are actually ahead  
14 of schedule, and I want this to be recorded.

15           Vernon.

16           DR. CHINCHILLI: I would like to make a suggestion  
17 that the Agency and the companies consider some equivalence  
18 trials. If the concern is about--

19           DR. HAMMER: It is already being done.

20           DR. CHINCHILLI: It is.

21           DR. HAMMER: Yes.

22           DR. CHINCHILLI: Can I elaborate?

23           DR. HAMMER: Yes, please.

24           DR. CHINCHILLI: Since there has been some concern

1 expressed about poor quality control groups, if the control  
2 group was the standard care or the best optimal three-drug  
3 combination, and then the experimental group, for instance,  
4 would be a three-drug combination where one of the drugs is  
5 the experimental drug, then, for one thing, if there is a  
6 treatment failure on the experimental therapy, then, the  
7 investigator could offer the alternative to the patient to  
8 switch to the standard of care drug.

9           So, in this way, there would be some control over-  
10 -some control, I realize it won't happen in every case--but  
11 it might minimize the amount of switching to alternative  
12 therapy. The switch would be to what is considered at the  
13 time to be the optimum therapy.

14           Of course, the Agency then is going to have to  
15 deal with issues like, well, what is going to be considered  
16 equivalent in terms of response, and I see Paul laughing  
17 over there, but I think it is worth the investigation, and I  
18 am glad to hear that it is being considered.

19           DR. MURRAY: We should just correct. I heard a  
20 statement, I guess maybe in the public hearing, that FDA  
21 requires superiority trials, and that is really not true. I  
22 mean equivalence trials are acceptable, and there has been  
23 at least one instance when an equivalence trial led to a  
24 drug approval.

1 DR. HAMMER: Thank you.

2 Fred.

3 DR. VALENTINE: It will be more complicated than  
4 equivalence trials in other areas, because if there is a  
5 failure, it may well be that during that time period,  
6 resistance has developed because of incomplete suppression  
7 to the other agents, and it is simply adding the one  
8 standard agent might still leave the patient in trouble.  
9 This is approachable with a lot of resistance, but it is  
10 going to be a little bit more difficult than with some other  
11 agents.

12 I wanted to make really one point, too, about  
13 something I said earlier, that is, a 1-log rise being  
14 counted as a failure of that regimen. I would put a second  
15 criteria - and achieve a certain level, that is, not going  
16 from 50 copies to 500 copies.

17 DR. HAMMER: So noted.

18 David, is there anything else? On that note,  
19 then, I would like to thank the Agency, the members of the  
20 committee, the audience, and particularly the presenters  
21 over the past two days, who really did a great job in giving  
22 us all this data to consume.

23 On that note, we are adjourned.

24 Thank you.

1                   [Whereupon, at 2:55 p.m., the proceedings were  
2 recessed to be resumed at 8:00 a.m., Wednesday, July 16,  
3 1997.]