

1 In models looking at resistance within individual
2 drug **classes**, resistance to PI was more predictive than
3 resistance to NRTI.

4 Thank you.

5 DR. HAMMER: Thank you very much
6 John?

7 **Summary of Key Points**

8 DR. MELLORS: Thank you, Veronica.

9 [Slide.]

10 I would just to like conclude the session by
11 review of prospective studies in progress. There are quite
12 a few. They **are** listed here by name, location, design and
13 status. RESA 2026 is closed and will be presented at the
14 retrovirus conference. VIRA 3001 just went through an
15 interim analysis and the FDA has asked me to tantalize you
16 with three slides from that interim analysis.

17 CERT compares phenotyping/genotyping to standard
18 of care. It is fully enrolled. CTOG 575 is phenotyping
19 versus standard of care. It is enrolling. Nick Hellman
20 from ViroLogics told me this morning he thinks it is fully
21 enrolled. There is NARVAL, SEARCH, HAVANNA, which is a two-
22 by-two factorial design of genotyping versus phenotyping
23 versus standard of care. They are all enrolling.

24 ERA is a study in the UK, phenotype/genotype
25 versus standard of care. It is opening soon. A5076 is

1 phenotyping versus genotyping versus both. That is in
2 development. So there are really quite a number of studies
3 that are ongoing or planned.

4 [Slide.]

5 I would like to just spend the next few minutes to
6 present some preliminary results from VIRA 3001 which was an
7 open-label, randomized trial comparing the effect of
8 phenotyping, immediate phenotyping, on viral load compared
9 with standard of care.

10 [Slide.]

11 Here is the study design. Individuals were
12 screened. There were no therapy change permitted during the
13 screening period. After the baseline individuals received
14 treatment based on the Antivirogram or standard of care,
15 there were 274 patients enrolled and follow up was at 2, 4,
16 8, 12 and 16 weeks.

17 [Slide. 1

18 The patient population studied was prior therapy
19 history of two or more nucleosides and one PI, plasma viral
20 load above 2000 copies, stable regimen for one month prior
21 to screening and no prior phenotypic sensitivity testing.

22 [Slide.]

23 Here shows the interim analysis results. This is
24 the HIV RNA response in a modified ITT analysis showing all
25 the observed data.

1 Let me share with you that there are about 127
2 patients in this analysis. By modified ITT, is those that
3 dropped out before enrollment and treatment change--in other
4 words, those who dropped out during the screening period
5 were excluded from this analysis. They were balanced
6 between the phenotyping and non-phenotyping arm. This is
7 the median log change in baseline RNA.

8 What you can see in yellow is the control arm and,
9 in light blue, is the Antivirogram arm and at each of the
10 time points in this analysis, after week 4, there is a
11 statistically significant difference in the viral load
12 response amounting to half a log or greater.

13 [Slide.]

14 A more conservative analysis of the last
15 observation carried forward, we see similar results. The
16 control arm and antigram arm, again half a log difference or
17 more statistically significant at each time point. The
18 proportion undetectable at 16 weeks was 62 percent in the
19 Antivirogram arm and 33 percent in the control arm.

20 The sponsor, Glaxo Wellcome, and Neil Graham are
21 in the audience if individuals want to ask additional
22 questions about this data analysis.

23 [Slide.]

24 Let me just end by summarizing some key points. I
25 think the standardized reanalysis of the retrospective

1 studies has generally confirmed associations between
2 baseline genotype or phenotype and virologic response. The
3 small datasets has led to some variability in the point
4 estimates and broad confidence intervals but, nonetheless,
5 there is consistency after reanalysis.

6 The placebo intervention-based trials that you
7 have heard about support the clinical value of resistance
8 testing for selection of treatment regimens in experienced
9 patients and, lastly, the data accumulating from ongoing
10 clinical trials of improved and investigational agents will
11 refine the interpretation and improve the predictive value
12 of specific resistance test results.

13 [Slide.]

14 I would like to close by acknowledging the
15 tremendous effort that was put forth under very tight time
16 lines by all the investigators involved. I don't have
17 enough slides or time to acknowledge all of them. Some
18 individuals that were not mentioned were Richard Harrigan,
19 Andrew Zolopa and other individuals that you have heard
20 about who contributed datasets as well as their statistical
21 support staff.

22 Thank you.

23 DR. HAMMER: Thank you very much. On behalf of
24 the committee, we would like to really thank you and the
25 members of the RCG. It is really a privilege to see these

1 data first-hand and for the first time.

2 Why don't we continue with Dr. Aras to wrap up
3 this section. Then we will take a break and then we will
4 have a question period.

5 **Summary of Studies Analyzed by DAP:**

6 **Statistical Comments**

7 DR. ARAS: Good afternoon, once again.

8 [Slide.]

9 You recall the data analysis plan discussed
10 earlier by Dr. DeGruttola and Dr. Mellors. Briefly, the
11 virological failure, as to type dichotomous variable, is the
12 dependent variable and it is to be explained by independent
13 variables, namely baseline covariates.

14 This is achieved using a logistic regression
15 model. I will make a few comments here to remind ourselves
16 of the limitations of retrospective analysis. My first set
17 of comments are about odds ratios.

18 [Slide. 1

19 These are the covariates that are listed in the
20 data analysis plan. You have already seen them. The extent
21 to which a covariate explains the dependent variable is
22 captured through the odds ratio. Hence, let's remind
23 ourselves what is an odds ratio and its relationship to a
24 related concept, a relative risk.

25 [Slide.]

1 Here is a definition of relative risk. Let p_0 be
2 the chance of virological failure when a covariate is at a
3 given level and let p_1 be the change of virological failure
4 when a covariate is one unit higher than the previous level.
5 The relative risk is defined as the ratio of p_1 and p_0 .

6 For example, if the relative risk is 2, it means
7 that the chance of failure is twice as high when the
8 covariate is increased by one unit. The same interpretation
9 may not be shared by the odds ratio, as we will soon see.

10 [Slide.]

11 Relative risk is the quantity of interest but,
12 typically, not estimable from a retrospective study. Hence,
13 a related quantity odds ratio is many times looked. An odds
14 ratio is defined as the ratio of the odds of failure for the
15 covariate at a higher level versus the covariate at the
16 lower level.

17 The odds ratio can be estimated from a
18 retrospective study but may not be of interest, of itself.
19 When p_1 and p_0 are small, relative risk is approximately
20 equal to the odds ratios. In such a situation, an odds
21 ratio can be interpreted as a relative risk.

22 In the present situation, however, such an
23 interpretation of the odds ratio may not be possible since
24 p_1 and p_0 are not small for all of the covariates listed
25 in DAP. For some covariates in some of the studies, the

1 relative risk can be estimated directly since the
2 randomization scheme took into account the covariate by
3 stratification.

4 Treatment, for *example, is a stratified covariate
5 in VIRADAPT and GART.

6 [Slide.]

7 Here are a couple of graphs that describe the
8 relationship between odds ratios and relative risk. You can
9 see that when p_0 and p_1 are small, odds ratio and relative
10 risk are nearly the same. But, as p_0 and p_1 increase and
11 p_1 is much larger than p_0 , the gap between the two
12 concepts increase.

13 You can see, as an example, if p_1 is at 0.5 and
14 p_0 is at .025, the relative risk is 2 but the odds ratio is

15 If the gap is even larger, if the p_0 is, say, at 0.025,
16 p_1 and 0.75, then the risk is 3.0 but the odds ratio is
17 .0.

18 [Slide. 1

19 The same information as in the previous slide is
20 depicted here slightly differently. Here, again, you can
21 see that if p_0 is at 0.4 and the relative risk is at 2.0,
22 then the odds ratio is at 6.0, so it is exactly three times.
23 It is the odds ratios and not the relative risks that are
24 generated by DAP methodology.

25 One is cautioned here not to interpret odds ratios

1 as relative risk.

2 [Slide.]

3 Let's move on to discuss the crucial table 1 in
4 DAP. Table 1 in DAP titled Mutations Associated with
5 Resistance to Specific Antiretroviral Drugs is the crucial
6 table there. It is largely based on in vitro data and/or
7 exploratory subgroup analysis. A general consensus is yet to
8 emerge on this table.

9 [Slide.]

10 Most of the studies were available to the
11 Resistance Collaborative Group before the DAP was developed.
12 Hence, in principle, a possibility exists that the DAP and,
13 in particular, table 1, was developed interactively to fit
14 the studies. We recognize that these are useful and valid
15 exploratory practices to generate specific hypotheses that
16 could be tested in confirmatory studies later.

17 With this caveat, let's look at some of the
18 results of these retrospective studies.

19 [Slide.]

20 For illustration, I have chosen only a few of the
21 models from those listed in DAP. Actually, these slides are
22 very similar to Dr. Miller's presentation and reiterate his
23 findings; hence, I will move through them quickly.

24 Model C has only one covariate, namely genotypic
25 sensitivity score whereas model E is a multivariate model in

1 which the odds ratios for genotypic sensitivity score are
2 computed in the presence of other covariates; namely, new
3 drug covariates and baseline log HIV-1 RNA.

4 The x axis represents the odds ratio. The y axis
5 lists the retrospective studies. The vertical line is the
6 odds ratio equal to 1. In all these figures, dropouts as
7 failures is depicted. The analysis was similar for dropouts
8 as censored.

9 The 95 percent confidence interval entirely on one
10 side of the vertical line at 1 indicates statistical
11 significance for that odds ratio. More adjustment for
12 multiple comparisons are made here. Notice that the
13 multivariate model, in most cases, has generated slightly
14 wider devices and hence, sometimes, the statistical
15 significance is lost. But, overall, you see the same
16 consistency that Dr. Miller pointed out.

17 [Slide.]

18 Here we have the 95 percent confidence intervals
19 for the number of PI mutations. The number of studies vary
20 across the slides since data was either not available to us
21 on all the covariates on the studies or a specific covariate
22 was not relevant in a given study.

23 [Slide.]

24 Here we have confidence intervals for odds ratios
25 with phenotypic sensitivity score as the predictive

1 covariate, again a univariate setup and a multivariate
2 setup. The SA minimum cutoff is the phenotypic that has
3 been looked at.

4 [Slide.]

5 These exploratory analyses suggest a predictive
6 link between virological failure and genotypic and
7 phenotypic measures at the baseline. They will provide
8 insight in generating specific hypotheses to be tested in
9 future confirmatory studies. We look forward to the results
10 of DAP from ongoing prospective studies that Dr. Mellors
11 mentioned.

12 Thank you.

13 DR. RAMMER: Thank you very much.

14 This was really very impressive. In order to
15 avoid the risk of the data-overload meter getting into the
16 red zone, I am going to suggest that we take a twenty-minute
17 break and return at 3:30-ish.

18 [Break.]

19 DR. RAMMER: I would like to officially reconvene
20 the committee session for this afternoon. We will do this
21 in two parts. The first will be a little bit of a
22 discussion of the data presentations and some clarifications
23 with questions and discussion, and then there are questions
24 specifically for the advisory committee to consider that we
25 will bring to open discussion.

1 I would like to initiate the second half of this
2 afternoon's session by asking Dr. DeGruttola, perhaps, to
3 comment on some of the statistical issues that were raised
4 in Dr. Aras' presentation: Perhaps we can have some
5 clarification for the group based on some of the issues that
6 we didn't have a chance to discuss.

7 DR. DeGRUTTOLA: There are a couple of issues that
8 Dr. Aras raised. As he correctly pointed out, an odds ratio
9 is not a risk ratio and shouldn't be interpreted that way.
10 So if you see an odds ratio of 2, you shouldn't say the risk
11 had doubled unless the risk was, in fact, very small.

12 On the other hand, as Dr. Andrew Phillips was just
13 pointing out, it isn't true that, in this case, we were
14 required to use an odds ratio rather than a risk ratio
15 because this was a retrospective study. If, in fact, we had
16 been confident that we could collect all the data that would
17 allow us to get not only whether or not there was a
18 virologic failure but the time of virologic failure, it
19 would be possible, from the retrospective data, to get a
20 risk ratio.

21 The reason we didn't was twofold. One was the
22 primary goal. was to get consistent analysis across all the
23 range of studies and keep things as simple as possible.
24 From that perspective, it make more sense to define a yes/no
25 variable of virologic or not rather than trying to find

1 exactly when those failures would occur, which can get
2 pretty complicated.

3 The other thing is that it was easier to do the
4 adjustments that we spoke of for baseline covariates, new-
5 treatment covariates, et cetera, by keeping it as a
6 dichotomous variable. And odds ratio is, we thought, the
7 appropriate way to present data when you have a dichotomous
8 outcome. Although you cannot interpret the odds ratio as a
9 risk ratio, as we have said, it is, nonetheless, a valid
10 measure of association between the covariates and the
11 outcome and that is why it was used.

12 On the second point, to what extent that Dr. Aras
13 mentioned--to what extent was the DAP developed specifically
14 in response to some of the features of the individual
15 datasets regarding the mutations that were important. Was
16 it the case, for example, that investigators knew that the
17 215 mutation was important in six of these studies, and
18 therefore, we wanted to make sure to get the 215 mutation
19 into the table to confirm what we already knew?

20 I don't think that describes the process at all.
21 I think that the table of mutations was based on experience
22 of virologists and investigators over a broad range of
23 studies and did not reflect just what was important in these
24 individual studies.

25 So I think that this analysis does move closer to

1 the kind of confirmatory analysis that Dr. Aras mentioned
2 rather than simply an exploratory analysis although I would
3 agree with Dr. Aras that we need to apply this methodology
4 'to other studies where the data haven't even been developed
5 yet to try to learn more about the association between these
6 different clusters of mutations and outcome.

7 But, in this particular case, the tables were not
8 developed based on specific knowledge about these studies.
9 In fact, I think the fact that we get fairly consistent
10 results across the studies even though the mutations that
11 were important in those studies was highly variable, the
12 nature of the drugs being used and so on tends to support
13 the value of these analyses as providing some confirmation.

14 But, perhaps, Dr. Mellors or Dr. D'Aquila would
15 like to comment further on the development of the table.

16 DR. MELLORS: I think, Victor, you have described
17 the process well. It had very little to do with the studies
18 to be reanalyzed. This was, really, a collective consensus
19 of, Rich, how many individuals, a dozen or more--a dozen or
20 more individuals some of whom had no, really, knowledge of
21 the studies that were even to be reanalyzed. I think is the
22 important thing.

23 The other important thing is that, in terms of the
24 phenotypic analysis, we used the assay minimum cutoff that
25 was defined by the company and that seemed to be validated

1 in this study. That was done without knowledge of the
2 phenotypic information from the reanalyzed studies.

3 Maybe Rich would like to add some subtlety or
4 major point that I have missed.

5 DR. D'AQUILA: Richard D'Aquila, Mass General
6 Hospital, Boston. No; I don't think anybody missed anything
7 major. I just wanted to point out another aspect of what
8 was mentioned about the mutation. There were different
9 people involved in these exchange of e-mails, both
10 virologists and clinicians.

11 I think the bulk of the data that led to defining
12 these mutations came from in vitro studies of site-directed
13 mutants with the specific mutations. I think some of the
14 people who were involved in these discussions were also
15 aware of clinical data that correlated viral load responses
16 with specific mutations, but I think the bulk of the
17 information really came from study of site-directed mutants
18 in vitro and I think that data is relevant and essential.

19 DR. HAMMER: Thank you.

20 Dr. Aras, did you have any other questions that
21 you would wish to have clarified?

22 DR. ARAS: Yes. I do agree with most of you. The
23 data shows tremendous consistency. I did agree with that.
24 My only fear was that, in the epidemiology of rare diseases,
25 typically logistic regression is fitted and there odds ratio

1 and relative risk are one and the same because the
2 probabilities are very small.

3 We did see a couple of speakers who did talk about
4 odds ratio as a five-fold increase, three-fold increase. So
5 there is a tendency there. I just wanted to point that out.

6 DR. HAMMER: It is important.

7 DR. ARAS: Just to keep that in our mind.

8 DR. HAMMER: Thank you.

9 Before we get to the six questions that have been
10 addressed to the committee, I would like to give the
11 committee members a chance to ask some questions. Once
12 again, I would like to thank the speakers that we had this
13 afternoon and the privilege to hear the VIRADAPT, GART and
14 RCG analyses here and particularly some of the new data
15 analyses that have not been presented anywhere else
16 previously. All of that is quite a privilege.

17 It also created data overload to some extent so it
18 is a bit hard to absorb everything from the RCG analysis in
19 this large group setting and frame questions but I would,
20 perhaps, in order to first have some takeaway point beyond
21 the consistency of the analyses maybe to ask Dr. Mellors one
22 question.

23 If one could look at some of the resistance
24 analyses that were included in the analysis plan which was
25 on phenotype four-fold and ten-fold cutoff, a genotypic

1 susceptibility score, numbers of resistance mutations, are
2 you willing to make a broad conclusion as to relative
3 prioritization of the predictability and relationship to
4 outcome for those measures across the studies.

5 I think some of us can draw conclusions from those
6 slides but they went by quickly and you know the data better
7 than anyone.

8 DR. MELLORS: I think the GSS and the PSS were the
9 most consistent. I think that we were limited in the
10 individual class genotype or phenotype by the number of
11 studies that could look at that. I did not show anything
12 for NNRTIs because there were only two studies that could
13 analyze that.

14 I think the take-home message from the DAP
15 analysis is that some score related to genotype or phenotype
16 is very important for determining response. I think it is
17 not just the DAP. It is John Baxter's GART. It is other
18 studies that have looked at it. It is prospective and
19 retrospective. But I would say that those two fell out most
20 importantly.

21 DR. YOGEV: Can I follow up with that. Did you
22 make a correlation between the GSS and the PSS?

23 DR. MELLORS: No; not in this analysis. There was
24 no analysis of the relation between GSS and PSS.

25 DR. YOGEV: Are there any plans to do that? The

1 reason I ask is it may be more practical because phenotype
2 today is a thousand and the genotype is cheaper. Should one
3 just go to one, two? This is a practical issue more than
4 scientific.

5 DR. MELLORS: There is no reason we can't do
6 correlations. You saw some data earlier today from ACTG
7 372. I think Doug Richman summarized it very nicely. The
8 correlation will never be 1.0 because the virus is always a
9 little bit ahead of us. But, as databases build, we can
10 improve the correlation. This is one dataset that can be
11 used but it is a relatively small dataset.

12 DR. HAMMER: Clarifying questions, again on the
13 afternoon's presentations.

14 DR. WONG: John, I was very impressed that the
15 data really seem to be very consistent. But I am concerned
16 that they are aggregate data, kind of all drugs at a time
17 analyzed together, study by study.

18 Can you tease out from all of the studies that
19 were analyzed in the metaanalysis any conclusions about
20 individual drugs by crossing through studies and looking at
21 individual drugs.

22 DR. MELLORS: The one study that looked at an
23 individual drug was the abacavir pooled data. Otherwise, I
24 think we are limited again by what is the lack of frequency
25 or the low frequency and number of studies in which a drug

1 was used consistently. So it makes it different.

2 We could look at classes and, depending on the
3 prior treatment experience and what was used in the new
4 regimen, we saw, in the example of ACTG 333, a very
5 important relation between protease and response to
6 saquinavir or indinavir.

7 So there are, within the aggregate data, examples
8 of individual response, abacavir, saquinavir, indinavir.
9 The problem gets into the fact that new therapies,
10 particularly in experienced patients, are not going to look
11 at individual drugs. They are going to look at
12 combinations. We talked about that this morning and it is a
13 problem.

14 So there are bits and pieces but we can't make
15 statements about each of the fourteen antiretrovirals; no.

16 DR. HAMMER: I guess it is fair to say that, even
17 with certain studies like 372 where individual drugs were
18 looked at in relation to virologic response in the study-
19 specific analysis, no relationship was found although a
20 summary measure of susceptibility, there was a correlation.
21 So, in fact, within a study you can look at the question you
22 raised. In fact, it creates the complexity of needing a
23 summary measure of susceptibility in combination regimens or
24 at least looking to that as helpful.

25 DR. MELLORS: I think Scott raised an excellent

1 point that I missed. In 372, the relationship between
2 individual drug susceptibility and response was not
3 apparent. It is only in aggregate that we see a correlation
4 with response because the response is dependent not on
5 single drugs but multiple drugs.

6 DR. POMERANTZ: I am going to let John sit down,
7 finally. Two of the trials gave some very surprising
8 findings. The one was led by Dr. Khaled and the other one
9 by Veronica Miller, Dr. Miller. The one by Khaled showed
10 that when you looked at phenotypic analysis for virologic
11 failure that the four-fold rather than ten-fold difference
12 was statistically significant.

13 Then, when you looked at the one by Miller, either
14 four or ten-fold phenotypic differences were statistically
15 significant. Now, based on this morning's discussion, I am
16 sort of surprised at that because part of that is trying to
17 dissect out what is a level of phenotypic resistance that
18 has clinical correlates. This is some of the first that
19 showed a true cutoff.

20 Maybe Doug or Dr. Little would like to comment on
21 these two trials.

22 DR. RICHMAN: Those conclusions are, to some
23 extent, a function of the population on whom--the data that
24 Dr. Ait-Khaled showed was that the ten-fold cutoff, this 80
25 or 90 percent of the patients, didn't fit about that

1 threshold so that there is no discriminatory power to show a
2 difference while the data of Dr. Miller, that breakpoint
3 might have been different so you have had the discriminatory
4 power.

5 So I don't think that that observation that his
6 data showed a difference between four and ten addresses the
7 question about individual drugs. I think we know from the
8 abacavir monotherapy data that probably four or six-fold is
9 enough to kill it.

10 With a number of drugs, I think you just need a
11 few-fold to probably make it inadequate but there may be
12 others in which that threshold, you have more margin of
13 error and you can have a higher cutoff.

14 So there are two points. I think, in general,
15 four-fold has more discriminatory power and clearly was as
16 good or better in all of these studies but for making
17 decisions about individual drugs, we still need more data
18 except we have the benefit of the abacavir which had a lot
19 of monotherapy experience that they could look at
20 retrospectively.

21 That is not a privilege or an opportunity we are
22 going to have with future drugs, I hope.

23 DR. POMERANTZ: Maybe we will talk about it more
24 tomorrow, but then why pick tenfold as a cutoff for true
25 resistance rather than four-fold or three-fold.

1 DR. RICHMAN: No; I wasn't. The reason the
2 analysis had two different cutoffs is because we didn't know
3 what the right one was and we were interested in finding
4 out. I think one other point that has been mentioned is the
5 pharmacologic issue where, with, for example, a number of
6 the protease inhibitors that have significant pharmacologic
7 enhancement by ritonavir, as monotherapy, a low level may be
8 enough to bump them off where you may be able to get away
9 with a higher level with ritonavir.

10 But that is the type of information that is going
11 to have to be generated in study designs in order to
12 convince all of us that that is true.

13 DR. POMERANTZ: I still remain a little bit
14 confused. If you were to look now at phenotypic analyses
15 and pick it, this is a resistant virus, this is not a
16 resistant virus, would you pick it at four-fold for most
17 drugs?

18 DR. RICHMAN: If I were managing a patient and got
19 some phenotype results, I would try to pick a combination of
20 drugs that were all less than four-fold. But, if I had no
21 choices--

22 DR. POMERANTZ: Thank you.

23 DR. HAMMER: Perhaps Dr. Ait-Khaled and Miller
24 might want to comment since their studies were mentioned.

25 DR. MELLORS: Roger, I think we have to be careful

1 in this analysis. The important thing I tried to stress was
2 that the point estimates are not that different between
3 four- and ten-fold. The confidence interval is greater
4 because the proportion of individuals who have greater than
5 ten-fold resistance is smaller.

6 When we are dealing with tiny datasets of 50 and
7 70 patients, the confidence interval can result in it
8 intersection 1 and the holy grail of the p-value is lost.
9 But I don't think we should be too swayed by that. I think
10 if you look in the 2007 study that the point estimates were
11 very similar between four- and ten-fold.

12 So I really think--maybe Victor would like to
13 comment on that, agree or disagree. The other thing--I
14 think Doug said it. For many of the approved drugs,
15 particularly the approved PIs, a four-fold change in
16 susceptibility may be critical because, at trough, there may
17 be three- to five-fold trough to IC50 ratio.

18 With a newer generation of protease inhibitors,
19 ten-fold may not be the cutoff. It may be thirty.

20 DR. DeGRUTTOLA: Just to comment briefly. I agree
21 with what John said. I wanted to go back to what the
22 objective of the DAP was, too, which was just to say that
23 you could find these summary scores, either phenotype or
24 genotype, that did show an association between the testing
25 and the response to the drug.

1 They are obviously not intended to try and resolve
2 the question of what is the cutoff, either the best cutoff
3 overall or the best cutoff for individual drugs, which is
4 going to take a lot more intensive research.

5 DR. HAMMER: Other clarifying questions?

6 DR. GULICK: A question for John Mellors. The GSS
7 relies a lot of table 1. You implied in your presentation
8 that this table engendered a lot of controversy to settle on
9 what it was. One of the critiques from the agency was that
10 there is no general consensus on the mutations in table 1.

11 How do we reach consensus on this and how close
12 are we to reaching consensus on a chart like table 1?

13 DR. MELLORS: I think it depends on who you are
14 trying to reach consensus with. At home, it might be
15 relatively easy but, in a complicated field like HIV, I
16 think it is very, very difficult.

17 And we will never reach consensus on every
18 mutation in a mutation table probably while we are still
19 breathing. I think, though, that we will hammer down--no
20 pun intended--mutations that have been shown in studies to
21 be related to outcome.

22 They will be black-and-white ones, as Doug said.
23 They will be grey ones and they will be highly contested
24 ones. So I don't think we are close to reaching a
25 consensus.

1 DR. HAMMER: Wouldn't it be fair to say that the
2 controversy does not extend to the whole table, that 80
3 percent of that table was probably easily reached and that
4 it was the fine points, if you will, of particular mutations
5 and particular drugs that led to the endless debate, or near
6 endless debate, that ended today. Is that fair?

7 DR. GULICK: That was my next question. so you
8 think 80 percent is pretty solid?

9 DR. MELLORS: I think that probably 80--yes; 80
10 percent or higher.

11 DR. RICHMAN: A lot of the mutations were, as a
12 participant in this 500 to 1000 e-mail exchange over a
13 couple-of-week-period, these are talmudic debates over
14 whether something is a primary or secondary mutation in
15 protease, and it is the seventh or eighth most important--
16 you know. Where do you put it on the table because the
17 whole analysis plan, if something goes up or down one point,
18 if it is on one side or the other.

19 But most of the debates were over three or four
20 little things here or there, should 3TC resistance--how do
21 you deal with that with adefovir. In general, we agreed on
22 almost everything.

23 DR. HAMMER: We should give Dr. D'Aquila a chance
24 to make a comment.

25 DR. D'AQUILA: The way I think we will reach

1 consensus is over time to build large databases that look at
2 genotypes and phenotypes on the one hand and viral-load
3 responses on the other.

4 I think we are just beginning to build those kinds
5 of databases. What we need are correlations now with the in
6 vitro behavior of the virus but how well we can treat it
7 with our current regimen. Those databases will take a long
8 time to develop and they will never be static because our
9 drugs will keep changing.

10 DR. JACKSON: Just a couple of questions on the
11 VIRADAPT and the GART study in terms of the turnaround time
12 of the genotype or phenotypic assays, how long that actually
13 took. Clearly, this virus evolves over days and a lot over
14 weeks. With the better assays, maybe we are underestimating
15 the effect if we get these back fast.

16 I don't know how long it took to get these back.
17 And then one other question was that, on the other hand,
18 against that, there seems to be no difference, as you
19 pointed out, in CD4 levels between the two arms later which
20 makes you wonder whether there is going to be a clinical
21 benefit of those.

22 DR. BAXTER: The average turnaround time was about
23 twenty-one days and the average time to randomization was
24 four weeks. In terms of the CD4-count issue, we found that
25 patients benefitted from GART regardless of their CD4 count,

1 whether they were between 50 and 200, and 200 to 500.

2 DR. JACKSON: When you say the "benefitted--"

3 DR. HAMMER: I think he was talking about the CD4
4 response in the two arms, not the baseline stratification.

5 DR. BAXTER: Oh, right. Part of that effect, in
6 the GART arm--there was more hydroxyurea used in the GART
7 arm which could have blended the CD4 response for those
8 patients, but also it was a very short-term study. It was
9 twelve weeks.

10 DR. HAMMER: Short-term pilot proof of hypothesis,
11 if you will; right?

12 DR. BAXTER: Right. We were really looking at
13 viral-load outcome.

14 DR. CLEVENBERGH: For the VIRADAPT, the turnover
15 time at the beginning of the study was quite long, about
16 four weeks. But now, we get the results in less than two
17 weeks. About the CD4, there was a wide range of variation
18 between the patients and also all the patients are already
19 on the PI regimen which has been shown to increase already
20 the CD4 even if the viral load was raised, so maybe there is
21 a confounding effect.

22 DR. PETTINELLI: I have a question for Victor. I
23 notice that in the different models, baseline CD4 was not
24 one of the covariates. Is there a reason for that?

25 DR. DeGRUTTOLA: I think it might have been

1 interesting to look at baseline CD4 and to look at other
2 possible confounders as well, but the main goal here was to
3 try and get an analysis plan that was as simple as possible
4 that really could be conducted in a fairly short period of
5 time consistently rather than to try and do analyses of
6 everything that was potentially of importance.

7 Given that we wanted to include one primary
8 indicator of patient status, baseline HIV RNA was selected.
9 Obviously, with our treatment, virologic failure of
10 treatment being the primary endpoint that was expected to be
11 the most important.

12 DR. HAMMER: Thank you. I think we should move on
13 to the questions that are before the committee.

14 **Questions to the Advisory Committee**

15 There are six questions, a couple of which we, perhaps, can
16 consider together. I will read them for the record.

17 The first question is, for use in drug
18 development, what are some important principles for
19 developing algorithms that classify mutational
20 constellations as "drug resistant?" How should mutational
21 algorithms and/or phenotypic breakpoints be developed in the
22 future?

23 This is quite a question, or two questions. Who
24 would like to tackle this? Again, not everyone at once,
25 here.

1 DR. MAYERS: I would agree with Rich D'Aquila. I
2 think, for the short term, what genotypes you like,
3 phenotypes, is what we can do. But what we ultimately want
4 is what correlates with failure to respond to the drug or to
5 loss of response to a drug.

6 So I think that the ultimate goal would be to get
7 genotypes and clinical and phenotypic breakpoints that
8 correlate with loss of antiviral activity of your drug, if
9 you can acquire that. The issue is going to be how to do
10 that in the context of combination therapies.

11 The other issue, which I think is going to come
12 into here is that all failure is not resistance and how you
13 discriminate the patients who have decided that your drug is
14 too toxic to live with from the patients who are failing
15 virologically is not necessarily easy.

16 So some level of compliance or looking at drug
17 exposure is going to have to be factored in when you make
18 those breakpoints. Otherwise, you can, for many drugs, mix
19 in patients who have stopped taking the drug because it is
20 too difficult with patients who are losing the activity of
21 the drug because of drug resistance.

22 Somehow, the company is going to have to factor
23 both of those into their analyses of breakpoint
24 determinations.

25 DR. HAMMER: You put your finger on the key issue.

1 How do you develop these algorithms in the current context
2 of combination therapy and the inability, and appropriate
3 inability, to add a single agent to background therapy and
4 tease this out.

5 DR. MAYERS: I think that, probably, you are going
6 to get more data from the patients who are failing, who have
7 been experienced, where you can, perhaps, see the mutations
8 that you have lost with your drug because the other drugs
9 may not be contributing much.

10 But you are going to have to analyze it in the
11 context of the other drugs the patients are receiving. That
12 is not going to be easy, as you said. I think that, looking
13 at your naive patients who are on the drug and failing will
14 have some use, but the problem may be--for example, with a
15 protease inhibitor, what you will find is that all your
16 patients are failing with 3TC resistance which might make
17 the company happy but isn't going to answer the question as
18 to what causes you to lose the drug.

19 DR. HAMMER: I think one point that comes out is
20 the first failure in naive subjects who have wild-type virus
21 at baseline will, depending upon which drug you are testing,
22 you might be able to tease out where the resistance is and
23 it might be the test drug, in fact, because it depends on
24 the genetic barrier. So the first failure may give you a
25 fair amount of information, depending, of course, on what is

1 the drug of interest.

2 Other comments?

3 DR. YOGEV: I just wonder if you take a naive
4 patient who starts breaking through and then starts to level
5 off at a certain level, isn't that a population for
6 resistance because there is some selection, maybe by the
7 virus, to go with one resistant and not for all the three or
8 four drugs which you are using.

9 So I would suggest that, if you have--you can
10 tease out who is taking the drug for toxicity. Hopefully,
11 we develop better mechanisms for compliance to see those out
12 and then you have to take those who are just coming out of
13 begin--suppose the drug is effective--and then start moving
14 away from it. The is maybe the time to tease out.

15 We know, by consensus, hopefully we will develop
16 sometime what the mutations are for the drugs which are not
17 new, to look into the other mutations and see if there is
18 any repetition of one. That is how we develop the
19 resistance now, knowledge. So there is no reason not to do
20 that.

21 Also, I thought that, in vitro, you can develop
22 the resistance in vitro by increasing different factors to
23 at least identify what part of the 1500 or 2000, whatever
24 you are going to screen, would be of interest to look in
25 that variation.

1 So I think the company should maybe supply, in the
2 developing of the drug, what is the resistant development in
3 vitro to then look later in vivo for this variation.

4 DR. HAMMER: Other comments?

5 DR. MATHEWS: There are some modeling things that
6 I am sure the investigators probably dealt with but didn't
7 have time to discuss. There is an assumption that there is
8 a linear relationship, the way the variables were coded and
9 the creating of the GSS and the PSS. So you don't really
10 get a sense of the explanatory power of that compared to
11 other ways of categorizing the variable, the cutpoints and
12 whether there is a ceiling effect and so on.

13 And model discrimination and calibration; were
14 those things looked at?

15 DR. DeGRUTTOLA: I think that that is a very
16 important point. I think what we have to keep in mind is
17 that, in developing these algorithms, there are two
18 approaches. There is sort of an exploratory approach where
19 you are trying to find out are there any new mutations that
20 you don't know about, how are these mutations interacting
21 when they affect the response to a drug, and confirmatory
22 analyses where you just trying to show that, with some kind
23 of metric you have developed, there actually is the
24 relationship that you think should exist.

25 As Dr. Mathews just pointed out, the analyses that

1 we did here were quite straightforward. We weren't trying
2 to model the specifics of the relationship between the
3 development or the presence of certain mutations or the
4 phenotype and the response.

5 In order to do that kind of modeling using
6 something that really might be appropriate, look for
7 nonlinearities, look for threshold effects, ceiling effects,
8 and so on, you would need a lot more information. I think,
9 to proceed with two different kinds of analyses, the more
10 exploratory one in which you don't set up all the rules of
11 the analysis in advance but you really try and let the data
12 sort of speak to you about what is going on to try and
13 understand these relationships.

14 Then, when you do understand them, you sort of
15 iterate and then say we are going to take what we now
16 believe is the appropriate model and apply it to another
17 dataset.

18 In this particular case, once again, these
19 analyses are done very quickly in the course of a month and
20 the size of the datasets were small. So we really couldn't
21 investigate in that period of time with this information,
22 the question that Dr. Mathews raised.

23 But, as Richard D'Aquila mentioned, only by
24 developing large databases and really trying to mine them
25 for this information, can that be addressed.

1 DR. MAYERS: Victor, before you sit down, do you
2 think, with the datasets and the analysis that you did, it
3 would be possible, over time, to develop parameters for each
4 of the individual drugs in the model for response models
5 such that when a new drug came long, you could potentially
6 use all the data you had previously accumulated for
7 predictions for the individual drugs and the regimen to try
8 and then get the parameters for the new drugs that you are
9 evaluating?

10 DR. DeGRUTTOLA: I think there are two parts to
11 that question. The first part is it appropriate to tease
12 out the mutations that are associated with each drug and to
13 view them separately. As long as those mutations don't
14 interact in the way that they affect the response to
15 treatment, that is a reasonable thing to do.

16 ' But, as I understood this morning's presentations
17 and others, sometimes they do interact. For example, the
18 184V mutation has different effects on different drugs. So
19 it may not be appropriate to try and look at the
20 relationship between each drug and each mutation but to look
21 at the relationship between patterns of mutations and the
22 combinations of drugs.

23 To the extent that that is not true, that you can
24 tease them out and allocate the mutations to specific drugs,
25 then you certainly can use the information in these data and

1 other data sources to try and do that. That should provide
2 a big help. Even if it is not perfectly true that they are
3 completely independent should provide a big help towards
4 understanding what is going on with a new drug.

5 DR. HAMMER: I don't think we have been
6 particularly helpful, but let me try to summarize question 1
7 for the agency. This may stimulate discussion or additions,
8 but we also need to move on.

9 The issue of developing algorithms and other
10 important principles, I think one thing to keep in mind is
11 the history here and that the table that we have been
12 discussing and other similar tables have benefitted by the
13 history of drug development and some of the limitations of
14 that because, during serial areas of monotherapy or addition
15 of single drugs that allowed the mutational patterns to be
16 evolved and defined, and it is has been iterated several
17 times but needs to be reiterated that that is going to
18 become more and more difficult.

19 However, it would seem to me that the basic
20 principles derived from what we talked about this morning
21 from a number of different ways. First, the in vitro
22 selection studies that will done for new drugs and
23 development and the mutations that are seen in vitro and
24 their proof of what they do by site-directed mutagenesis,
25 those basic virology assays are important.

1 The testing of new drugs against panels of viruses
2 with characterized mutational backgrounds including
3 multidrug resistant profiles is important. Obviously, the
4 good characterization of isolates from patients who fail
5 therapy and taking good looks at those viruses in vitro and
6 testing them, Looking at the mutational patterns, testing
7 those mutations in site-directed mutagenesis assays and
8 phenotyping them are all important.

9 I think it is also important to mention that
10 relational databases are also going to help us,
11 organizations. Both commercial and academic are involved in
12 developing large relational databases that will help us
13 determine, or at least make hypotheses about what certain
14 patterns will look like for resistance to the drug of
15 interest and for cross-resistance.

16 We didn't really talk about breakpoint issues, and
17 that is part of this question. But I think that essentially
18 has been answered that nobody knows the breakpoints. What
19 we know, at least for phenotypic assays, what individual
20 assay performance can tell us, is what is the cutoff level
21 at which there is a clear, statistically proven difference
22 against a control isolate.

23 But how that translates to activity in vivo is a
24 complex issue related to the particular susceptibility of
25 the drug, the susceptibility of the isolate and the drug

1 exposure. I think one thing, perhaps, to reiterate, is that
2 we do need more and more data about achievable levels in
3 vivo and be able to relate IC50s or IC90s or IC95s to that
4 and then make some determination of how many fold above that
5 we want to be.

6 So I think no simple answer about determination of
7 breakpoints can come but just as MICs are different for
8 various bacterial agents in relation to achievable levels
9 and activity of drugs, et cetera, the same thing holds here.

10 Does anyone want to add to that modest summary?
11 Dr. Murray is not happy.

12 DR. MURRAY: No; I am happy with it. I just
13 wanted to know logistically if anybody would like to comment
14 who and how could this be accomplished. Should it be left
15 up to the sponsors to develop their own individual
16 breakpoint for their drugs? Ideally, would it be nice to
17 have a committee?

18 DR. HAMMER: I wasn't really being facetious
19 earlier when I mentioned the NCCLS because I actually think
20 that, at some point in our development, we need to bring a
21 consensus body together to try to actually put a dataset
22 together that can be used and built upon.

23 That would be my own feeling.

24 DR. CHARACHE: I am also on the NCCLS direction at
25 this point. They have just been working, as you know, on

1 susceptibility testing for other viruses. Some of the
2 thoughts might be helpful putting in here.

3 But I did want to add just the practical
4 consideration that it really will be key to standardize the
5 methodology that is used to determine phenotypic breakpoints
6 or whatever of the IC50s and IC90s because I am not certain,
7 in some of the various reports we have heard today, whether
8 all are using the same methods. It is the details that
9 would make a difference between the results and whether four
10 times or ten times makes a difference.

11 DR. HAMMER: I would just say that, of the two
12 recombinant methodologies that are out there, the first-
13 level cutoff and the second-level cutoff vary with the
14 manufacturer but they are clearly definable and, I think,
15 well characterized on an assay-performance basis. They
16 differ slightly one to the other, but they are pretty clear
17 cut.

18 Does anyone else want to comment on Dr. Murray's
19 question?

20 DR. IACONO-CONNORS: Before we move on, I just
21 wanted to ask the committee sort of a basic question. It is
22 a little bit backwards but with respect to all the genotypic
23 data we have been hearing about today, I am curious as to
24 whether we should be thinking about any mutations in terms
25 of their linkages.

1 Most of the data that we see, it is all
2 population-based sequencing so we really don't have a sense
3 of their linkage. I wonder if any of the speakers have an
4 opinion on whether we should be concerned about this.

5 DR. HAMMER: Since the question was first directed
6 to the speakers, does anyone want to talk about that?

7 DR. D'AQUILA: I do have a few slides about that
8 in the talk for tomorrow morning, but just to directly
9 address it, to date, there is good evidence that population
10 sequencing is adequate for detecting linkage.

11 DR. HAMMER: Other questions or comments on No. 1
12 before we move on?

13 Question 2, which I think we can deal with
14 reasonably quickly as far as targeted responses are, in
15 addition to the covariates and methodology for assessing
16 treatment response included in the DAP, what additional
17 covariates or methodologies should be considered when
18 evaluating resistance data.

19 I think some statistical input and other clinical
20 research input is important here. Dr. Pettinelli already
21 raised the issue of the CD4 count. Who would like to add to
22 this?

23 DR. MASUR: One of the correlates that I guess I
24 am not clear about in terms of pharmacology is we seem to be
25 relaying everything to Cmin in terms of the likelihood of

1 response. Is it unequivocal that Cmin, rather than area
2 under the curve or some other pharmacologic variable, is the
3 correlate that we want when we are looking for correlating
4 drug levels to the likelihood of response?

5 DR. HAMMER: I will turn to Dr. Fletcher as the
6 resident expert on this committee.

7 DR. FLETCHER: No; I don't think it is. I think,
8 for the three classes of drugs that are available, I
9 wouldn't be surprised that it is not different for each
10 class of drug. I am persuaded that, for the PIs, troughs
11 are important. For the non-nucleosides, I am not. There is
12 some data on troughs but also area under the curve.

13 For the nucleosides, where the active moiety is
14 the intracellular triphosphate, I am still really not sure
15 what it might be. I think this is one of the real
16 challenges, as you try to move forward.

17 Virology and pharmacology here, I think, are
18 fundamentally intertwined. That doesn't mean that you have
19 to absolutely understand exactly how to move forward with
20 virology, but I think if you want to have a vision for
21 optimal patient management and being able to understand
22 everything that contributes to it, we are going to have to
23 lay out a plan so that we can quantitatively understand what
24 does pharmacology contribute, what does adherence
25 contribute, immunology and so on.

1 So back the pharmacology, I think one of the real
2 challenges is trying to understand what metric is it that is
3 going to tell you the most about response.

4 DR. MASUR: I guess, then, the corollary to this
5 is it is just going to be too complicated, as we sort out
6 the correlation of genotyping and phenotyping to failure, to
7 make sure that patients are, in fact, failing in the
8 presence of adequate drug or whether they are failing for
9 other reasons.

10 There is going to be a lot of background noise
11 here when the patients are failing for all the reasons that
12 a number of speakers have pointed out other than lack of
13 activity of the drug, but are we just going to have to
14 accept all that as background noise that we are going to
15 have to surmount with these assays?

16 DR. FLETCHER: I think initially you might because
17 just the virologic data alone, I am fairly persuaded that
18 phenotype and genotype information contributes to the
19 information on why you have success or failure. I think
20 that question is can you do better if you add additional
21 information into that.

22 I don't know to what degree--for example, take the
23 CNA2007 study where there is an adverse interaction between
24 amprenavir and efavirenz. In the back of my mind, is that,
25 somehow, contributing to this difference between a fourfold

1 resistance falling out and a ten-fold not.

2 I can't come up with how it might be but I keep
3 wondering about what confounders that may be adding. I
4 think you have to lay out a plan to start somewhere.

5 DR. HAMILTON: It strikes me that there is a
6 variable that we haven't heard much of anything about
7 concerning the durability of the benefit conferred by
8 genotypic testing. What we have are relatively short-term
9 studies and a limited number of tricks in our bag.

10 I wonder if there are not some projections that
11 have been made about what happens next. Do we go back to
12 time zero and the same series of events happen again? Or
13 are we in a better position or what? I am not even now
14 talking necessarily, although I could be persuaded to talk
15 about it, what the long-term implications are here. I am
16 talking just about recurrence of viral loads at relatively
17 higher levels.

18 DR. JOLSON: It is a very important point. I
19 don't think we have the data to answer that. It all relates
20 to what the armamentarium is going to be at the second and
21 third and fourth round. But a hint of that, of the utility
22 of resistance testing on the second round, at least, is from
23 the open phase of the VIRADAPT study where the deferred use
24 of genotyping allowed a response in the second six months.

25 Now, that is an open phase of that study but,

1 again, it says that something is up even when you use
2 genotyping in a deferred fashion. So, to me, that is
3 encouraging although obviously not proof in a randomized
4 fashion over a strategic trial over three or four years.

5 DR. MAYERS: I think an issue, as we try and
6 relate pharmacology to resistance is going to be that we are
7 going to have an agreed-upon methodology for protein-
8 adjusted IC95s or IC50s because it is clear that these drugs
9 have very different protein binding and it is free drug that
10 is important so that if you are going to try and relate and
11 IC95 in a relatively protein-free culture media with the
12 patient's blood, you are going to have to do the adjustment
13 and it would be nice to actually get an agreed-upon method
14 of adjusting drugs for their protein binding and then to be
15 able to make the correlation between IC90 in a test tube and
16 drug levels attained in the patient.

17 DR. HAMMER: Let me ask Dr. Fletcher a follow up
18 to that. It is obviously important but even it is more
19 complicated. It is not just the free drug but it is the off
20 rate and the protein binding, the tightness of the binding
21 that may influence it, not just the proportion of free drug
22 versus bound drug. Is that correct or not correct?

23 DR. FLETCHER: It is. When you get into some of
24 the multiple, let's say, PI-PI combination or a PI-non-new
25 combination where you now have two highly protein-bound

1 drugs, I don't think we understand can there be, then--if
2 they are bound to the same binding site, can there be
3 competition.

4 I suspect that the final best way to sort that out
5 will actually be quantitation of the unbound concentrations
6 in plasma.

7 DR. RAMMER: Let me ask Dr. Murray a question
8 related to the question that has been put to us because the
9 question includes the specifics of the DAP and the issues of
10 covariates and methodologies, particularly statistical
11 methodologies.

12 Are you referring specifically to the RCG analysis
13 that we have seen and how those data should be looked at
14 more thoroughly or in the next round or is this a more
15 generic statement about other covariates that should be
16 looked at because the RCG and the DAP is a very specific
17 project?

18 I don't know if this is a project-specific
19 question or a more generic question that is being placed to
20 us.

21 DR. MURRAY: I think it was a more generic
22 question for analyzing data that might come to the committee
23 in the form of maybe even an NDA for a new drug where they
24 want to include resistance data, just standardizing ways for
25 evaluating resistance data in the future.

1 DR. HAMMER: I would just mention a few things.
2 Again, it depends on the dataset. I think Dr. DeGruttola
3 made it very clear as to the streamlined nature of this for
4 the purposes at hand. To bring all these datasets together,
5 streamlining was critical.

6 Other baseline covariates besides what Dr.
7 Pettinelli mentioned; obviously, gender, age, some of the
8 normal demographics would have to be looked at even if one
9 doesn't suspect that there is going to be much of an issue.
10 But I think subtype and other virologic characteristics as
11 we move into more spread of viruses beyond group B around
12 the world into areas where there is drug development going
13 on are going to be important to look at.

14 But I don't know if there are any statistical
15 issues that Dr. Woolson, maybe you want to comment on?

16 DR. WOOLSON: I think one thing is, as Dr.
17 DeGruttola had mentioned, that the intent with the Data
18 Analysis Plan was to have an overall summary the would work
19 across a number of studies. If we are talking specifically
20 about projects that would come before our committee for
21 review, I think it really is good for us not to lose sight
22 of the fact that the continuous variables, like the log of
23 the HIV RNA, actually provide very valuable information.

24 We saw a number of the presentations today where
25 we had a dichotomy based on failure--for example, the GART

1 summary--and also had the actual log of the HIV RNA. I
2 think that information, in terms of those changes, is very
3 valuable. The Data Analysis Plan, as I understand it now,
4 doesn't speak directly to hanging on to those values, but I
5 would imagine that, as they go through future iterations,
6 they will probably look at other kinds of endpoints.

7 But I think that is one issue, that we would need
8 to, I think, continue to focus on the continuous variables.
9 At least, I think that is very important.

10 The other issue I wanted to raise about the data
11 analysis, and maybe this is more of a specific question to
12 Victor, is the very last slide that was up, and I think that
13 does deal with question 2, as well, for us. Your very last
14 slide indicated how you would apply these, this Data
15 Analysis Plan, to intervention studies.

16 You didn't mention specifically that you would
17 look at a treatment by these covariate interactions yet, in
18 some of the studies that were presented today, there were
19 some very clear treatments by covariate interactions.
20 Again, I was assuming that that was something would be
21 worked out at a later point.

22 DR. DeGRUTTOLA: I think those issues are very
23 important. But I think it would have to be left to the
24 investigators of GART and VIRADAPT to work out those
25 interactions and present them for those studies. Again, the

1 purpose of this was to just come up with an analysis that
2 could be applied consistently across studies with a very
3 pointed question for the issues that you raised.

4 I think the investigators could probably best do
5 that on their own and, as you mentioned, some of those
6 points were addressed in their presentations.

7 DR. PETTINELLI: I might just say the obvious, but
8 when you were looking at covariates in modeling, I think we
9 also have to make sure that we have the right number of
10 patients to look at because I was a little bit concerned,
11 for example, for some of the statements that were made
12 following the analysis of the Frankfort cohort which stated
13 that when you are looking at--like, resistance to PI was
14 more predictive than resistance than NRTI, to look at the
15 confidence interval at least when we are looking for fold
16 differences.

17 That is the difference. I don't know if it is
18 because there are less patients, there is variability. So,
19 what I am saying is we have to be careful in terms of what
20 we are working with.

21 DR. MATHEWS: Jeff's question reminded me that,
22 very often, the committee and the division have to look at
23 several studies in different populations to evaluate a
24 product for licensure. In the future, if claims are going
25 to be made that a product is effective in the setting of a

1 certain mutational pattern, you are going to have to be able
2 to make cross-study comparisons even within the same NDA
3 application.

4 That means, based on some of the VIRADAPT data and
5 other studies we haven't talked about yet, that there has to
6 be comparability in variables like adherence and drug levels
7 and those kinds of things which are increasingly being
8 incorporated into clinical trials but are not uniformly
9 there.

10 Now, for example, there is data already that
11 adherence, itself, can make over a log and a half
12 difference, a population at three or six months which is
13 larger than the effects that were described for genotyping
14 testing.

15 So I think that these things are covariates that
16 need to be looked at and incorporated up front in some
17 standardized fashion into clinical trials. It also affects
18 the issue of poolability for large cross-study comparisons
19 like what was presented this afternoon because, unless those
20 things are standardized in some way, they will just increase
21 the overall variability and the quality of the studies is
22 not the same.

23 DR. YOGEV: I just wondered, from the modeling, we
24 are almost accepting now that less than 400 is the cutpoint.
25 The clinical studies suggested there is a negative effect,

1 even if you have about 50. So shouldn't the modeling be
2 changed to go to 50 as a prediction of failure to try to
3 find that resistance that maybe there are earlier in that
4 system than waiting for the 400 which is a convenience which
5 I think we should leave at point.

6 DR. HAMMER: Just on your comment on the RCG, I
7 think 400 was taken because it was an endpoint that could be
8 seen across all of these studies and it wasn't making a
9 statement that that is the way that all of these analyses
10 should be done.

11 DR. YOGEV: I have no quarrel with what was done,
12 I am saying, for the future, what covariate to look at. I
13 was wondering should we just also lower the modeling for
14 if future presentation to go to 50. We know that when we say
15 50, we are still in the billions in the body. So maybe we
16 need to go even lower. But, at this point, I think that
17 already 50 for the future study, not for what was done.

18 DR. HAMMER: Any other comments on question 2 as
19 far as far as covariates are concerned and resistance data?
20 I am not sure I can really summarize this for the agency. I
21 think some of the issues have been obvious, that the
22 populations need to be well defined. RNA has been mentioned
23 and was already included. Obviously, CD4, basic
24 demographics, gender, age, viral subtype is important where
25 the populations expand and, I think, most importantly, the

1 covariates of drug exposure or measures of drug exposure,
2 adherence and PK.

3 I am also thinking, taking Dr. Mathews statement
4 one step further in what he said earlier today, whether one
5 is looking at resistance retrospectively in a study,
6 particularly in a substudy, or in a prospective fashion for
7 drug that is being developed specifically to go after
8 resistant virus.

9 I think some of the issues of defining the
10 populations and powering the studies appropriately are
11 important when these are done in a prospective fashion to
12 prove a drug's validity and efficacy in a drug-resistant
13 population rather than in retrospective studies.

14 More and more we will see that as drugs that look
15 particularly good as salvage agents come through.

16 Any additions to that?

17 MR. HARRINGTON: Scott, just one. I want to just
18 go back to what Dr. Hamilton said how the patients are doing
19 now. Ideally, if you have these huge, large relational
20 databases, it would nice to know how the patients are
21 actually doing physically, clinically. That would be nice.

22 DR. HAMMER: I don't think anyone would argue with
23 that. At least one of the relational databases that I am
24 aware of doesn't really have that kind of clinical follow-up
25 data but certain groups can develop that and should develop

1 it, certainly, in the academic environment where people are
2 being entered through clinical trials and long-term follow-
3 up is being attempted.

4 DR. STANLEY: I just want to add to the things
5 that can contribute to resistance that are not intrinsic to
6 the virus. We have to keep in mind it hasn't been a big
7 issue for us so far in HIV virology, but if we go back to
8 other infectious diseases, thinking about things like Dr.
9 Richman mentioned this morning, proton pumps and other
10 things that may be intrinsic to the cells or limiting
11 nutrients in the cells or other things like that.

12 Presumably, that would try to be controlled for in
13 the in vitro preclinical stage, but those are other non-
14 viral intrinsic resistance factors.

15 DR. HAMMER: Thank you. I think we are going to
16 see a wave of information about that in the Nature and
17 Medicine report.

18 We are going to move on to questions 3 and 4 which
19 I think we can combine since they are identical except for
20 one word; do the data presented support the clinical utility
21 of HIV genotypic testing for use in drug development. That
22 is question 3. Question 4 is identical replacing genotyping
23 testing with phenotypic testing.

24 This is an easier question, at least to me, it is.
25 Who would like to start this discussion?

1 DR. YOGEV: Yes.

2 DR. JACKSON: Just to play the devil's advocate
3 here, though, based on the prospective studies of the
4 VIRADAPT and the GART study, one could argue, getting back
5 to this adherence issue, these were open-label studies. I
6 assume that the patients knew whether they were on the study
7 arm or the control arm and whether that may have made a
8 difference in adherence in a claim, this difference.

9 There were also differences in the study group.
10 Not only did they have the benefit of GART but they had the
11 benefit of expert opinion that was based, not just on the
12 GART results, but on the antiretroviral history.

13 If the control arm had had the benefit of expert
14 opinion, just based on the antiretroviral history, would
15 that have made a potential difference. There are also no
16 differences in CD4 counts by the different arms, as we have
17 already mentioned.

18 These were relatively sick populations with about
19 200 CD4 counts. Whether this really will clinically benefit
20 this relatively sick population, I am not sure the data is
21 really there to say that. My personal opinion is I think it
22 probably will, but the data are the data and there are these
23 potential confounders that I think we can't ignore.

24 DR. RAMMER: Just to add to that, I think the per-
25 proportion below the copy number limit chosen in VIRADAPT

1 and GART at 12 weeks actually is not dissimilar than
2 salvage-regimen studies whether it be 359 or 372 that were
3 doing it without prospective testing. But I think, again,
4 these were pilot groups of hypotheses studies and it
5 relates, again, to the armamentarium used.

6 But the data are consistent. I think this
7 question, I would say, although potentially primarily driven
8 by the prospective studies, our thinking needs to be
9 influenced by the new prospective study on phenotyping that
10 we got a glimpse of here but also the retrospective analyses
11 that are pretty consistent.

12 You have to ask yourself has any study shown the
13 negative that the application of resistance testing leads to
14 a worse outcome.

15 The people who wouldn't speak into the microphone
16 were murmuring budgetarily and financially.

17 DR. GULICK: Just to follow up on what you just
18 said, Scott. At first glance, it is disappointing that the
19 best arms in VIRADAPT and GART have rates that are very
20 similar to the early salvage studies where we didn't have
21 the benefit of resistance testing.

22 But then when you go back and look at the studies
23 that you mentioned, 372, 359 even CNAA 2007, what they have
24 in common, as a big success rate, are people that were non-
25 nuke naive and then got a new nucleoside. So you wonder if

1 that what it balances it out.

2 DR. HAMMER: It also brings up that it is more
3 than just having a resistance test and someone to interpret
4 it. It is intervening at the right moment at the lower
5 viral load rather than a higher viral load, choosing the
6 right drugs, et cetera. It is complex, as everything in
7 this disease is.

8 DR. MAYERS: I don't think the clinical management
9 question is what the FDA asked here. What they asked is
10 what is useful in drug development and understanding how
11 your drug succeeds and fails and, perhaps, defining
12 populations that your drug would be better suited to and not
13 suited to.

14 I think, for that area, the answer is yes and yes.
15 And then, for how we use the test and who should use them
16 and when, I think the answer is a bit more open. But for
17 the drug-development issue, I think the answers are fairly
18 clearly "yes" and "no."

19 DR. HAMMER: Although I think they are interlinked
20 because the drug development process is going to use the
21 application of resistance testing to either do
22 randomizations up front or strategically use the drug in a
23 population that fails. The immediate derivative of that,
24 again, which we will talk about tomorrow, is the clinical
25 application. So I think these are somewhat inextricably

1 linked.

2 But the question is, specifically, in drug
3 development which, if anything, should make Dr. Jackson more
4 happy about saying "yes" without the words in his mouth.

5 DR. PETTINELLI: I also agree that we are ready to
6 use the genotypic and phenotypic testing drug development.
7 I really refer to our discussion this morning which was
8 presented by Doug in terms of where and when. Again, the
9 characterization of post-treatment isolates, is important,
10 most important, to try the specific patients that were
11 failing, particularly if the drug is presenting some very
12 positive effect over the specific use and population.

13 DR. HAMMER: Any other additions? We did touch a
14 little bit, as Carla mentioned, on this question earlier
15 this morning looking at applications in phase I and phase
16 II-III.

17 I think this is easy to summarize. The questions
18 3 and 4 are "yes" and "yes."

19 Question 5. What are the limitations of the data
20 correlating mutational patterns with clinical income?
21 Clinical outcome; thank you. It brings us back, full
22 circle, to the psychologic issues that were raised this
23 morning that I am quite suggestible when someone mentions
24 financial matters in my ear next to me, here. Both are
25 true, however.

1 Who would like to talk about this, clinical
2 outcome and mutational patterns.

3 DR. PETTINELLI: To me, the major limitation today
4 is that we have only short-term data and I think it is very
5 important to develop a long-term database. I don't know if
6 the several studies that are ongoing that were discussed
7 earlier, indeed, there was the duration. But I think that
8 would be important.

9 DR. JOLSON: I just had a quick follow-up question
10 to Carla's to direct to Dr. Mellors. In terms of the
11 prospective ongoing studies that you showed, can you just
12 give us a general sense of how large they are and how long
13 the follow-up is of patients so we can kind of expect what
14 might be coming with additional data?

15 DR. MELLORS: They range in size from a couple of
16 hundred to over 500. Follow up is as far as 48 weeks. But
17 that is the initial protocol. It could be extended.

18 DR. HAMMER: Can I ask a follow-up question, John?
19 RCG, phase II, **as** far as analyzing the database further but,
20 also, with the number of prospective trials that you have,
21 in follow-up to Dr. Jolson's question, of bringing analyses
22 together for prospective trials looks interesting, as well
23 as longer-term follow up in a cooperative fashion.

24 DR. MELLORS: The RCG is holding out for a
25 retirement package, a pension, similar to what you get in

1 the military. So, we haven't talked about phase II. We are
2 not quite done with phase I until tomorrow at 5:30. As Doug
3 said, we were hoping to declare victory and disband.

4 DR. HAMMER: But you can be reborn with another
5 acronym.

6 DR. MELLORS: It will take more than that.

7 DR. MASUR: Just to follow up on what Mark
8 Harrington said before. This question asks what are the
9 limitations regarding mutational patterns with clinical
10 outcome. I guess, at this point during the day, we have
11 accepted the fact that clinical outcome equates to virologic
12 status whereas, in fact, clinical outcome is obviously a
13 much more complex issue.

14 When we talk about the limitations of data
15 concerning the correlation with clinical outcome, I guess
16 the question is do we really have some way of looking at
17 whether or not the patient is better off far down the road
18 in ways 'other than simply virologic load, or in terms of a
19 long-term strategy.

20 DR. POMERANTZ: I think that is a very important
21 point. We talked about it a little bit yesterday as well as
22 this morning is that clearly it would be great if we could
23 everyone to undetectable or to profoundly decrease their
24 viral load. I think everyone, now, would agree with that.
25 But with a lot of these salvage therapies where the

1 genotypic and phenotypic analyses are going to be used, you
2 are not going to be able to do that, at least in this first
3 generation or second generation of drugs that we have.

4 So there are these patients that are being more
5 and more described, some anecdotally, some non-anecdotally,
6 that do not get a great benefit in the CD4 count, do not
7 have profound changes in their viral load, yet seem to do
8 fairly well and may do better than those that did not have
9 changes in their antiretrovirals.

10 I think that was the point is that we are not only
11 going to follow viral load but, as this goes out, I think
12 you are going to see this disconnect in certain patients
13 where some will do better than you might think just looking
14 at the viral load and CD4 count.

15 Understanding those parameters on a basic
16 biological level is important but understanding them
17 clinically with these correlations is going to be very
18 important because a lot of these people will not have great
19 changes in the viral load as these studies sometimes have
20 shown even this afternoon.

21 So I would just reiterate that and say that I
22 think that you are going to have more of that problem rather
23 than less of it.

24 DR. MAYERS: I want to stay away from the issue of
25 long-term benefit of resistance testing. On the other hand,

1 there is another resource. Both the ACTG and, I think, the
2 CTCRA have large mutation datasets now. We are going to
3 have over 1200 patients fairly soon in CTCRA and every one
4 of them is enrolled in the clinical-endpoint long-term
5 monitoring study.

6 So I think the issue of other mutational patterns
7 that would be better or worse against the true clinical
8 data, virological data, will be emerging over the next few
9 years in both the ACTG and the CTCRA and, if we are truly
10 smart, we will make the datasets meldable.

11 DR. KUMAR: I want to follow up what Dr. Pomerantz
12 just said. We continue to see in clinical practice a number
13 of patients who clearly have failed therapy by all
14 measurements that they are set for but continue to do
15 clinically well.

16 I am not sure taking the genotype testing and
17 altering the antiretroviral treatment without looking into
18 toxicity data, quality-of-life measurements, that we are
19 really doing them a service. Without looking into those
20 type of data whether we can say yes. On a short-term basis,
21 there is clearly a decline in viral load. Whether that
22 includes the long-term benefits, I really don't think we
23 know as yet.

24 DR. HAMMER: Although I would just make a plea. I
25 agree we need cohorts and long-term follow up and to see the

1 fruits of what we are doing over the next five to seven
2 years in a more cohesive fashion, I don't think we are
3 suggesting, or can go back or should go back to clinical
4 endpoint issues here.

5 At least that is my own feeling. I think what is
6 being raised is, in fact, the fact of discordance and viral
7 fitness issues and replicative capacity when viruses are
8 impaired. But even some of the groups that have reported
9 discordant responses and hanging up of CD4 counts and
10 clinical benefit, clinical status patients that have
11 remained well over time despite virologic failure are now
12 beginning to demonstrate that those patients do go on to
13 failure immunologically as well.

14 So those data will emerge. But I think it is
15 complicated because viral load doesn't tell you everything
16 pathogenetically that is going on and you need to look at
17 other factors. I think that is what we are saying and it is
18 getting more complex than some of the issues about whether
19 certain mutations impair the virus more than others is
20 clearly important and one of the limitations, I think, in
21 response to this question.

22 Hopefully, we will stimulate some discussion.

23 DR. MAYERS: I think there has been a confusion
24 between the strategy of using a resistance test--let's just
25 make it generic--a resistance test to manage patients, the

1 strategy of using a resistance test to manage patients every
2 time a viral load becomes detectable.

3 I think that is a very different issue. I think
4 that you have two--it looks like three prospective studies
5 that show that when you make the decision that it is time to
6 change drugs, the testing will help you to get your patient-
7 -your patient is twice as likely to go below the limits of
8 detection with the test than without out.

9 But that is very different than how you choose the
10 test and at what time you choose the test so that it is
11 quite rational to let people float through for two years
12 with discordance in viral load and do nothing. But when you
13 decide you want to change therapies, I think, at least in
14 the short term, you are twice as likely to get undetectable
15 with genotyping or phenotyping, per your preference, at that
16 point that you choose to change.

17 So it is going to be hard to address that in any
18 serious way for long-term clinical benefit.

19 DR. HAMMER: Personally, I agree. I think we are
20 falling a little into the trap, which is obviously easy in
21 discussions like this and is the same thing we did with
22 viral load. Everyone focussed on a number. We can't focus
23 on a resistance result and think that you are going to
24 manage an HIV patient properly if that is the only thing you
25 are thinking about.

1 DR. HAMILTON: This just actually emphasizes the
2 point I wanted to make which was that to extrapolate the
3 data that was presented today, as compelling and as
4 interesting and as important as it is--extrapolating that
5 information to the population at large, I think, would be a
6 big mistake at this moment.

7 I think we need a lot more information in terms of
8 how this actually benefits patient outcome in very real
9 terms. You can call them clinical endpoints if you like. I
10 call them life. I would like to think that what we are
11 doing is going to have a long-term impact.

12 How we go about measuring that, assessing it,
13 implementing the current set of guidelines that undoubtedly
14 will appear as a result of this impressive dataset is
15 another matter. But I think we do not want to lose sight of
16 the larger picture here.

17 DR. CHARACHE: I think, in terms of new-drug
18 development, a very key issue here is to define what is
19 meant by clinical outcome. Is it CD4 count? Is it other
20 parameters? I think this will have to be agreed upon.

21 DR. HAMMER: I am not sure, in this question,
22 whether it is marker RNA outcome, CD4 outcome or ultimate
23 clinical outcome. Some of us reserve clinical outcome for--
24 purely what is truly meant by that. I thought that was the
25 implication of the question.

1 DR. KAPLAN: One thing I have always been
2 impressed with in the GART data is, in a sense, it
3 represents kind of a real-life situation in that about half
4 of the providers in the GART arm didn't do exactly what they
5 were asked to do.

6 This happens in clinical practice. They make
7 their own judgments and so forth. In the study, which only
8 went out to week 12, the curves start to come together and
9 the percentage of patients that were undetectable becomes
10 insignificantly different in twelve weeks. So I think,
11 again, it raises the issue--here you have, perhaps, even a
12 short-term virologic benefit.

13 Now, VIRADAPT showed a longer term, but what
14 exactly does that short-term virologic benefit, just for
15 three months or so, mean in terms of a long-term endpoint
16 for the patient. I think we are hearing that over and over.
17 I wouldn't argue about the value of phenotypic or genotypic
18 testing and producing some virologic benefit, but question
19 No. 5 specifically says what are the limitations.

20 I think we are all owning up to what the
21 limitations are.

22 DR. MATHEWS: I think, also, and it is really not
23 a limitation since these are very preliminary analyses, but
24 I think the kind of confirmatory studies that Dr. DeGruttola
25 was talking about are really essential if this kind of data

1 is going to be useful. Develop a model in one study, apply
2 it to another dataset and see if it is equally predictive,
3 look at alternative parameterization of the measurements to
4 the scores that are developed and just, really, see if you
5 can get the biggest bang for the buck out of the data that
6 is already there.

7 That is going to take a lot of time and energy and
8 I certainly appreciate all the work that has already been
9 put into it but you can milk it for a great deal more.

10 DR. HAMMER: Let me just try to summarize
11 question 5. The limitations of the data correlating
12 mutation patterns with clinical income--clinical outcome.
13 (something else comes to mind in my new role outside of this
14 committee. Clinical divisional income is probably the thing
15 we deal with on the most frequent basis. It sounds like I
16 need to talk to John about his counseling.

17 The limitations, I think, in what we have seen
18 today, the data summarized, et cetera, relate to, I think,
19 some of the numbers we were--some of the studies don't sort
20 of have enough numbers within certain drug-class mutational
21 patterns to help us. So I think there are a number of
22 issues. Dr. Pettinelli raised the issue of follow up.

23 Obviously, resistance mutational interactions are
24 difficult, sometimes difficult, to infer from just looking
25 at mutational patterns and that is where phenotypic testing

1 comes in. We talked about that there may be impaired--what
2 these mutations are doing to the functional replicate of
3 capacity of the virus which there may be mutations which, if
4 just scored as mutations, may actually be helpful to the
5 patient by impairing the virus.

6 There are, obviously, issues of what we don't
7 know. It was only two-plus years ago that we didn't really
8 know--or at least I didn't know about the 69 insertion. And
9 then there was a wave of presentations at the Resistance
10 meeting, two meetings ago, and then just everywhere.

11 So there are other multidrug patterns that we are
12 going to need to know about. So there will always be
13 limitations on a mutational pattern as well as the fact that
14 we do not discover everything we need to discover unless we
15 start doing multiple clones on patients.

16 So there are many limitations but it doesn't, I
17 think, obviate the importance of defining the--it emphasizes
18 long-term follow up, it emphasizes the importance of
19 relational databases.

20 Other additions to that?

21 The last question is another classic ending
22 question for the day; what additional clinical studies are
23 needed to further define the clinical utility of resistance
24 testing? Dr. Mathews talked about that in relation to
25 datasets that currently exist and particularly in relation

1 to the RCG analysis, but would anyone like to add--

2 DR. STANLEY: I just to add the caveat, define the
3 clinical utility of resistance testing in drug development
4 which is, I think, what we are here for today. I think that
5 in studies that are planned that we need to take into
6 account the nonvirologic factors. I don't think it is too
7 much to ask of a drug company, if they are going to use
8 resistance testing to show data about their new drug, that
9 they show that they have accounted for absorption and the
10 pharmacokinetics and adherence and other issues.

11 DR. GULICK: One thing we haven't mentioned today;
12 every study that we have heard today, and this is a bit
13 tangential, but every study we have heard today took people
14 who were failing their regimen, did resistance testing and
15 then switched them to a new regimen immediately.

16 We have also been hearing, and I guess Veronica
17 Miller has presented some interesting data, about stopping
18 the so-called course of treatment interruption and using
19 resistance testing in the context of treatment interruption
20 to try to maximize future options.

21 I guess it is more of a clinical management, the
22 drug development question, but it directly speaks to the
23 question, I think.

24 MR. HARRINGTON: Just to follow up slightly on
25 what Trip said, if you can restore sensitivity to some drugs

1 during SGIs and you can also maybe get a more potent effect
2 on the salvage regimen which might actually make appealing
3 for companies to study the new agent in this population,
4 which is something that has been hard for to persuade
5 industry to do until now.

6 So, using the resistance test pre- and post-
7 treatment interruption would actually be very important.

8 DR. KAPLAN: In terms of what the question
9 specifically says, and what we have been talking about
10 today, drug-experienced patients and salvage therapy,
11 obviously, we need to study, to look at, other uses such as
12 in antiretroviral-naive persons. I presume we are going to
13 be getting into that tomorrow morning from what I am seeing
14 on the agenda, that there are such things going on but we
15 haven't even gotten into that area, the utility of
16 resistance testing in that arena.

17 DR. PETTINELLI: I think it would be important to
18 establish the relative utility of phenotypic versus
19 genotypic resistance assay. That is a little bit different
20 from drug development but I think, again, it would be
21 important to compare each other how they perform in terms of
22 outcome of the patient.

23 DR. HAMMER: Thank you. It looked like there were
24 some studies, some that I am aware of and others that I
25 wasn't aware of, that are listed on Dr. Mellors' slide of

1 prospective studies that are enrolling or have enrolled or
2 will enroll.

3 Other comments? I think we have really touched on
4 this. As far as further studies, I think the important
5 point that Dr. Stanley made about not just looking at
6 resistance but I think taking the VIRADAPT pharmacologic
7 study further that other cofactors are really important. I
8 think the pharmacology study within VIRADAPT is very
9 helpful, in fact, in showing that there are independent
10 predictive power to resistance testing and to optimal
11 levels, how they were defined in that study.

12 So other factors need to be prospectively defined
13 within studies. Within the context of defining the clinical
14 utility, we certainly have more retrospective analyses, but
15 I think the key will be in the prospective studies and with
16 the relation of drug development, it is going to be in
17 defined populations depending upon the drug and its
18 characteristics.

19 I think there are two ways--more than two ways--to
20 do this and one is, at baseline, as far as the population
21 that one recruits and one could, prospectively, do
22 resistance testing to see, as it evolves--one could
23 randomize on the basis of resistance testing if one has the
24 drug.

25 We talked about this before, that may be useful,

1 particularly with a particular genotype or phenotype. And
2 then one could use it strategically in a clinical trial as
3 far as management which gets into how long the benefit and
4 the continued benefit of resistance testing can be in first
5 failure, multiple failure and over time.

6 So I think the studies that we have seen so far,
7 retrospective and prospective, are really the tip of the
8 iceberg. As to how to apply them, it really is better-
9 defined populations, up-front randomizations, proper
10 stratifications, and use in a strategic fashion that will
11 tell us where these will ultimately be placed.

12 I think it is also worth stating philosophically
13 that, like every other assay in HIV care, it is here, it is
14 being used, it is out in front of how we know how to use it,
15 and that will be true of the next major assay in HIV as
16 well.

17 So I don't think we will actually ever catch up.
18 The technology is ahead of us. It has taught us a lot and
19 it will continue to tell us a lot, so I don't think we will
20 ever actually catch up with our clinical trials with the
21 advance in technology, and maybe that is a good thing.

22 Other statements or additions to question 6?

23 We are twenty-one minutes ahead of schedule. I
24 would ask Dr. Jolson or Dr. Murray what else you would like
25 is to --

1 DR. JOLSON: I just wanted to thank a moment to
2 thank all the invited speakers today and, also, in
3 particular to thank all of the people who helped put
4 together the DAP presentation. We recognize it is an
5 extraordinary amount of work. It was all done as part of a
6 cooperative effort.

7 It has been enormously helpful for us to see these
8 analyses. I think we have learned a lot from it. I really
9 can't thank you enough for the time and effort that went
10 into it.

11 I would also like to make just a personal appeal
12 not to disband the RCG after this because I think,
13 particularly as tomorrow's discussion evolves, it will
14 become clear that the issues are going to get more and more
15 complex as we start thinking of different scenarios to apply
16 to resistance testing and drug development.

17 It would be impossible for the agency to think
18 through these issues unilaterally. We really need comment
19 and participation by industry and academics and others
20 working in the field to help further the thinking. So that
21 would just be a personal appeal that there be some sort of
22 an ongoing effort to work collaboratively on that.

23 DR. HAMMER: I would echo that. I think that the
24 presentations were fantastic this afternoon, and impressive,
25 but, in no way, can they be absorbed by this committee or by

1 the agency within a couple of hours. I think that the data
2 need to be mulled over and thought about and there are whole
3 issues of analysis and interpretation that can help
4 understand resistance testing and its application on the
5 drug-development process.

6 So I would hope that there would be further
7 communications between the agency and the RCG and other
8 groups that have datasets that have datasets that have an
9 impact on this analysis. It has really been impressive.

10 So I would, in closing, thank the participants,
11 the speakers, the agency, our guests and consultants of the
12 committee and, really, everyone that put a lot of effort
13 into today's event. It is not over. Tomorrow is part 2 and
14 we welcome you back here at 8:30 tomorrow morning.

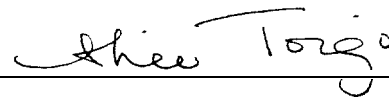
15 [Whereupon, at 5:15 p.m., the proceedings were
16 recessed, to be resumed at 8:30 a.m., Wednesday, November 3,
17 1999.1

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C E R T I F I C A T E

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



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