

National AIDS Treatment Advocacy Project

Report of Day 2 From FDA ADAC Hearing on Using Viral Load as an Endpoint in Studies **written by Jules Levin**

A series of presentations by the FDA and pharmaceutical industry researchers on July 15, the second day of this hearing, were followed by comments from David Feigal, the outgoing director of the Antiviral Drug Division of the FDA, comments from community representatives during the open session, and committee discussion.

Up until now disease progression (clinical events such as PCP, MAC, KS, etc.) and death were criteria for full FDA approval. Under the new FDA proposal a drug company can conduct either a clinical endpoint study or a viral load endpoint study for full approval. On July 15, David Feigal said companies can now submit viral load endpoint protocols for full approval to the FDA.

At the ACTG (AIDS Clinical Trials Group) meeting in Washington DC from July 19-22, it was announced that the ACTG would form a committee to consider changes they may need to make to the design of their trials in consideration of the proposed changes. We are in fact entering a historical transitional period if in fact viral load endpoints become a new primary measure of judging the merits for full approval.

Summary of selected highlights. Because the following report of the second day of the hearing is lengthy, it was requested that I summarize this report for those who may not want to read it in its entirety. But, there are a number of interesting details in the full text that cannot be included in the summary.

1. Length of trials. It was suggested that the same trial for accelerated approval could extend into one for full approval. The primary endpoints for both could be viral load based. The vast majority of panelists supported the concept of using viral load endpoints for a study aimed at full approval for a drug. They agreed that data is convincing that treatment effect on viral load adequately predicts clinical effect, although many expressed concern that viral load did not fully capture the clinical effect from treatment. Scott Hammer, the chair of ADAC, said 48 weeks is the absolute minimum length of a trial for full approval.
2. Labeling--a product will be labeled for its effect on viral load. Any labeling on clinical effect will require clinical data
3. The data presented indicated that baseline viral load and the nadir (the lowest level reached) of suppression of viral load reduction predict the durability of a reduction in viral load. The lower an individual's baseline viral the more likely they are to reach undetectable and to sustain it. Individuals with higher baseline viral load are less likely to reach and sustain undetectable. Generally, although not always, individuals with higher baseline viral load take longer to reach undetectable. The more reduction in viral load that you can achieve, the more durable the effect. In the Merck 035 study, 86% of the participants were below

400 copies/ml and 71% were below 50 copies/ml at 68 weeks; most who reach 400 also reach 50. And, the 15% in between remain under 400 copies/ml. In the Incas study, where treatment-naïve participants received nevirapine/AZT/ddI, unless an individual reached 20 copies/ml, they were unable to sustain the viral load reduction. Many researchers believe it is important to suppress viral load to below 50 copies/ml to attain durability, but the data supporting this is limited

Some research found baseline CD4 to be relevant to predicting treatment response and some research found it was not predictive. Even when it helped to predict it wasn't as relevant as baseline viral load. But, baseline CD4 considered with baseline viral load may increase the predictability

4. Time to treatment response, and durability. For an individual who eventually reaches undetectable, they may not reach a 1 log reduction in 4 weeks. The gradient of their decrease in viral load may be slower. Response to therapy is individual and treatment by providers must be individualized. It is crucial to give each individual ample opportunity to respond to therapy. Premature discontinuation from a treatment can be extremely harmful. However, this should be balanced with not leaving an individual on a regimen for too long without a satisfactory response. If not satisfied with treatment response, and if appropriate for the individual situation, intensification of the treatment is an option. In the Abbott/Roche trial #462 which studied ritonavir+saquinavir, 7 participants who did not reach undetectable intensified the regimen by adding d4T+3TC by 24 weeks. 6/7 remained undetectable at the latest checkpoint which was between 4-16 weeks of follow-up.

Additionally, it can take anywhere from 8-24 weeks for an individual to reach 400 copies/ml, although most reach that goal by 12-16 weeks. It will take a number of weeks longer to reach 50 copies. It can take as long as 28 weeks or even in some instances up to 12 months to reach 50 copies/ml. The amount of prior treatment-experience may also impact on the ability to reach and sustain "undetectable."

5. It is difficult to reach and sustain 400 copies/ml with double nucleoside therapy unless you have very low baseline viral load. Glaxo Wellcome presented data that 72% of treatment-naïve individuals with baseline viral load of 5,000 copies/ml or less were undetectable at 48 weeks, in a retrospective study they conducted consolidating data from 6 studies of AZT/3TC. However, with treatment experience and increasing levels of baseline viral load the percent under 400 copies/ml drops sharply. For example, for treatment-experienced study participants with baseline viral load between 20-30,000 copies/ml, 0% were under 400 copies/ml after 48 weeks.

If you accept that the goal of therapy should be to lower viral load to undetectable if possible, using double nucleoside therapy as your initial treatment is questionable. There appears to be general agreement among leaders in the HIV medical community that full suppression (undetectable) should be the goal of therapy. It is generally agreed that a potent 3 or 4 drug regimen will best reach that goal. However, initial therapy with a double-nucleoside regimen (AZT/3TC,

d4T/ddI, etc.) is still an option. David Feigal stated at the hearing that initial therapy with a double nucleoside regimen should be considered as a treatment option because of the concern of using up treatment options if resistance develops.

6. There was data presented suggesting that partial suppression of viral could be achieved. A portion of individuals were able to maintain a low level of viral load for a period of time. This subject is controversial. Some researchers are concerned that anything less than full suppression is harmful and may create irretrievable resistance. How can you pre-determine whose viral load can be partially suppressed without risking a sharp increase in viral load? Some researchers believe such maintenance is not possible for an adequate length of time. While, Fred Valentine, a panelist at the hearing from NYU Medical Center, suggested that the reason that some individuals were able to achieve partial suppression may be the predominance of wild-type virus in that situation, not resistant virus.
7. Finally, study designers will need to address certain important considerations for trial design including: how to characterize the magnitude of initial viral load reduction, time to response of treatment, time to loss of response, and durability of the response; how to address the varying responses to treatment; and other considerations for different types of study populations (eg - treatment experienced vs naive, early vs advanced disease, etc.)

Full Report

FDA. Paul Flyer of the FDA was the first speaker on July 15. He said, surrogate markers (HIV RNA) should predict clinical effect, and the greater the reductions in HIV RNA the lower the risk of disease progression and greater durability can be expected.

He said, the focus of this hearing for the use of viral load as a long term study endpoint is driven by its appeal as a direct measure of antiviral activity and the current emphasis in clinical care on achieving maximal suppression. It is proposed that the role of HIV RNA will be expanded beyond its use as a surrogate marker under accelerated approval to using it as a new type of treatment indication, which would be suppression of HIV RNA. This criteria would serve in a confirmatory trial for full approval of a new drug after accelerated approval was granted.

He said, a claim of clinical benefit will not be permitted without clinical data. It is not required that HIV RNA be accepted as a validated surrogate marker beyond that considered under accelerated approval. Labeling will have to be adjusted to reflect changes in trial requirements. Claims in a label may express approval granted based on effects on viral load and/or CD4. Trials of adequate size to detect differences in HIV RNA will also be large enough to detect differences in CD4.

Flyer went on to briefly address differing ways to use viral load and some of the special challenges confronting the design of trials including:

1. In the past we have used means over time to evaluate a drug. For example, the

mean or median reduction in HIV RNA over 24 or 16 weeks. At the FDA they have been using AUCMB (area under the curve minus baseline), which is a statistical method of measuring changes throughout the entire treatment period during a study for comparison of treatment effect between study groups and does not represent the actual change from baseline at a selected time point. If the goal of therapy is maximal suppression studying averages may not be the best way to summarize treatment effect when you really want to know the HIV RNA for a particular patient at a particular point in time

2. Another problem is the inability to actually quantify the amount of reduction in HIV RNA. For example, if 75% of study participants are below the level of quantification (undetectable) it is difficult to measure the actual reduction in HIV RNA.
3. Study participants will tend to switch therapy when HIV RNA and/or CD4 rebounds. The average change in HIV RNA over a fixed period of time may mask real treatment differences if a patient switched therapy during that time span
4. Characteristics of different patient populations require consideration of different trial designs. For example, individuals with lower baseline HIV RNA are more likely to reach undetectable and are likely to do so quickly. Individual differences in prior treatment experience, baseline CD4, and disease stage are additional considerations that can effect responses to treatment and may call for different considerations in trial design.

The pharmaceutical industry researchers, hopefully with the aid of the FDA and academic researchers, will be trying to devise workable trials designed to tackle these concerns.

The development process of several drugs are approaching the point of having to submit a study for full approval. The accelerated approval or New Drug Application (NDA) reviews are expected to occur in 1998 for DMP-266, 1592U89, bis-pom PMEA, and possibly 141W94. As well, Agouron has received accelerated approval for nelfinavir but their full approval study is ongoing; it compares ritonavir+2 nucleosides with nelfinavir+2 nucleosides. It will be interesting to see the trial designs suggested by the companies and approved for implementation by the FDA. As you may know, trials for full approval have to be underway or about to start at the time of review for accelerated approval.

Flyer said the goal should be to select ways to measure viral load that best capture the characterization of both magnitude and duration of viral suppression.

Since we are not merely interested in quantifying the amount of reduction in plasma viral load, a number of different ways to use viral load as an endpoint have been suggested for use as endpoints including: percent of individuals below detection which could be 400 or 50 copies/ml; the durability of these latter two measures; the time to virological failure; the time to treatment failure which could be measured by CD4 or clinically. A one log reduction in RNA from baseline may be characterized as an adequate virological response, and rebound of 0.5 log or back to baseline may be an acceptable

characterization of loss of virological response. Paul Flyer summarized the need as-- what is the best way to assess study treatment-induced changes in HIV-RNA, as well as changes in CD4 and disease progression to be able to adequately describe the long term treatment effects.

He expressed particular interest in the following types of measures of viral load changes: time to lack of virological response; initial response to therapy; virological failure. He said, "we have seen that the more pronounced the initial suppression the lower the risk of disease progression". The following pharmaceutical presentations include data addressing these points of interest.

Data from several drug company research efforts indicate that the nadir of viral load suppression appears to correlate with the durability of sustaining that suppression. That is, generally, the lower viral load is suppressed the more durable the effect is.

For example, in the Merck 035 study essentially the same of number individuals (86%) who were able to suppress viral load below detection (500 copies/ml) have remained below detection at 68 weeks; 71% were below 50 copies/ml at 68 weeks. Since 71 of the 86% are below 50 copies, that may indicate that it is necessary to lower viral load to 50 copies/ml in order to sustain a durable HIV RNA response.

Dale Kempf of Abbott Labs has presented data from a retrospective analysis of three ritonavir studies which suggests the same conclusion that the nadir of viral suppression dictates the durability of suppression. A review of this study is posted to the NATAP web site (drug development section; the data was initially reported by Kempf at the 4th Retrovirus Conference in January '97). As well, it is discussed in the current issue of our newsletter, NATAP Reports. In fact, he has stated that he believes suppression to below 20 copies/ml or even lower is probably the best way to attain durability, although researchers are just now trying to compile data to establish this theory. Of course, compliance with taking study meds is required for success with therapy.

And, as you will read below according to David Hall, unless you reached 20 copies/ml in the Incas study you were not able to sustain a durable HIV RNA response; reaching 400 copies/ml was not adequate to sustain a durable response.

Flyer raised the issue of how long a viral load endpoint trial should last to obtain full approval while saying that 48 weeks may be acceptable. However, myself as well as others from the community have expressed that data collection for efficacy, safety and clinical progression must be continually collected and analyzed way beyond 48 weeks. We need to know the effects of therapy extended out to at least 3, 5, and 10 years.

I think, in some form, studies will have to collect clinical data. It remains to be seen how this is integrated into the larger picture. It is possible that drug companies may want to conduct viral load endpoint studies for approval but follow them with some form of study aimed at collecting clinical endpoints. This will be difficult because traditional clinical endpoint studies are unlikely to be utilized. The question is what form of study can be both feasible and collect clinical events? There is considerable discussion about using treatment strategy trials for this purpose. However, ideas on how to design this type of

trial have been circulating for 1-2 years without any viable proposals yet emerging.

Pharmaceutical industry. Jeff Chodakewitz of Merck Labs said, based on his group's analysis of three indinavir studies, individuals with higher baseline viral load took longer to reach undetectable. You have to adjust expectations for individuals with higher baseline HIV RNA. This has been a theme starting at the St. Petersburg Resistance meeting, that individuals with higher baseline viral load take longer to reach undetectable, don't reach undetectable as often as those with lower viral load, and may need more potent therapy to reach and sustain undetectable (see preliminary analysis of ACTG 320 in report being prepared for web site now). In Chodakewitz' analysis, CD4, gender and race did not effect time to response. Chodakewitz and other presenters reported that it takes longer, sometimes several months longer, for individuals to reach below 50 copies after they've reached below 500 copies/ml.

The analysis of data presented by Chodakewitz was based on individuals with at least 24 weeks of plasma HIV RNA data who participated in one of three indinavir phase II/III studies: protocols 028, 033 or 035. The study participants received either nucleosides alone, indinavir monotherapy or a two or three drug combination including indinavir. This analysis focuses specifically on the treatment groups who received indinavir alone or in combination, and most of the combination therapy was with indinavir+AZT. The data or conclusions reached from this analysis may be limited in some instances by the fact that not all participants received a more optimal therapy of indinavir+2 nucleosides. Viral load measurements were done at baseline and every 4 weeks during the studies.

The definition chosen to characterize "responders" were those with two consecutive viral load measures below 500 copies/ml. Chodakewitz said this was a stringent definition but one that he thought was the best way to predict a durable response. This may in fact be an important consideration in defining ways to characterize initial viral load responses for trial design purposes.

56% of the study participants (204/356 individuals) for whom they had data met the definition. The analysis is based on these 204 individuals. The time to response was defined as the first time point in which a viral load below 500 copies/ml was observed. They had median baseline CD4 and viral load of about 200 cells and about 20,000 to 30,000 HIV RNA, and about half of the participants received combination therapy.

The analysis indicated that about 40-50% of those receiving indinavir alone were responders, by definition of two consecutive viral load measures below 500 copies/ml (remember that testing was conducted every 4 weeks), about 50-60% of those receiving indinavir+AZT were responders, and about 90% of those receiving triple therapy were responders. In the Merck 035 study, participants had prior AZT experience but were naive to 3TC and protease inhibitors. Their baseline CD4 and viral load were 142 cells and about 42,000 copies/ml. The only Individuals receiving triple-drug therapy including indinavir included in the analysis presented were participants in 035 and were treated with indinavir+AZT/3TC.

By week 4, about 60% of those individuals who were going to respond, and by week 8, 80% of those who were going to respond, had done so. However, it takes 20 weeks for all

the individuals who were going to respond to do so.

Chodakewitz said, when looking at participants who took longer to respond, 15-20% of at weeks 2 and 4 did not have even a 1 log decline in HIV RNA, and these were individuals who eventually responded. This delay in response may only be associated with using protease inhibitor therapy, and may not be associated with NNRTI or 2-nucleoside therapy which doesn't include a protease inhibitor. He said, this has important implications for clinical practice and for purposes of designing trials to detect adequate initial viral load response. This information indicates the risk in judging too soon that the therapy you're taking isn't working as well as you hoped. Conversely, not all participants who had large drops in viral load went to below 500 copies/ml. This raises the concern of not knowing how long to wait before realizing you may not be declining to below detection.

In the section called Criteria for Changing Therapy in the HHS Guidelines for Use of Antiretroviral Therapy, they say "specific criteria that should prompt consideration for changing therapy include: less than a 10-fold (1 log) reduction in plasma HIV RNA by 4 weeks following initiation of therapy"; and then they go on to list other criteria. This conflicts with Chodakewitz's information.

The draft HHS Guidelines are general recommendations. Treatment decision making in HIV is an individualized process. You cannot apply the same recommendations to all. The Guidelines do state in the introduction that these recommendations "are not intended to substitute for the judgment of a physician who is expert in the care of HIV-infected individuals," and the Guidelines should be helpful to such non-expert medical providers who may need them, but the danger is that medical practitioners may fail to individualize therapy decision making but just apply the guidelines blindly. But, as recognized by some experts in the treatment of HIV, individuals with HIV should only be treated by expert specialists since treatment has become much more complicated, just as cancer is treated by oncologists. We are at the point in the development of the treatment of HIV where medical practice in HIV should be regulated to require such expertise. Where is the Secretary of HHS, Donna Shalala, and the American Medical Association on this issue?

This apparent difference between how long it can take to realize a full response to therapy creates a challenge to the design of a trial. Barry Quart said treatment failure must be defined carefully to avoid switching patients that are still responding.

The concept of intensification of therapy is related to this scenario. In the Abbott protocol 462, which studied therapy with ritonavir+saquinavir alone, participants were followed closely with viral load measurements. When it was observed that an individual was not responding by a decline to below detection, in this case 200 copies/ml, the therapy regimen was intensified by adding d4T+3TC. 6/7 individuals who received the intensification fell to and have remained below 200 copies/ml for a follow-up period of 4-16 weeks. A detailed review of the latest 48-week data from this study is in the latest issue of our newsletter, [NATAP Reports](#).

In an analysis of responders in protocol 035 who declined to below 500 copies/ml, 42 participants received either indinavir alone or triple therapy including indinavir. 34 of the

42 also had viral load below 50 copies/ml using the ultra-sensitive assay. Chodakewitz said they felt comfortable using a cutoff of 50 copies/ml at the time of doing this analysis. It took about 16 weeks for all these individuals to fall below 500 copies/ml. But, it took considerably longer, 28 weeks, those who were going to fall below 50 copies/ml to actually do so. Suggesting, expectations of time to full response have to be adjusted based on baseline viral load and the assay being used.

Chodakewitz said, higher HIV RNA at baseline, a smaller initial drop in viral load, and a lower CD4 count did tend to be associated with a lower likelihood of declining to below 500 copies/ml.

As I stated, I think treatment decision making should be individualized. You cannot generally refer to the HHS Guidelines about to be issued and base your personal treatment decision upon such a general guideline. For example, the guidelines recommend for initial therapy a 3-drug regimen containing one potent protease inhibitor (indinavir, ritonavir or nelfinavir) plus two nucleosides (AZT, d4T, 3TC, ddI, ddC). But, if your baseline viral load is particularly high, you may want to consider a more potent regimen than 1 potent protease inhibitor+2 nucleosides; and, there are several available options that may fill that need. How you define a "particularly high viral load" can be a judgment call but several hundred thousand certainly is particularly high; in my opinion, a viral load of 100,000 may qualify as a high viral load which may call for a more potent regimen.

It was suggested at the June 1997 St. Petersburg Resistance, Strategies and Eradication Workshop, that individuals with higher baseline viral load and/or lower CD4 might need a more intense therapy regimen. Although some might disagree, I think the CD4 count is also relevant. A higher CD4 count may indicate a more intact immune system better capable of responding well to therapy. In fact, Chodakewitz did say, as referred to in the previous paragraph, lower CD4 tended to be associated with lower likelihood of lowering viral load to below 500 copies/ml.

Barry Quart, of Agouron Pharmaceuticals, was the next speaker and raised an issue others also thought was important. Is there an early response that might be predictive of the durability of a good response? He felt that the response in the first 6 months was a good indicator of what will occur in the next 6 months. Very few who are responders in first six months lose that response in the next 6 months. Again, looking at the Merck 035 and Incas data unless you reach 20 or 50 copies/ml durability was not sustained and it can take considerably longer to reach 50 than 400 copies. He said baseline CD4 was not relevant to durability of HIV RNA response, although Chodakewitz said lower CD4 at baseline was associated with less of a likelihood of declining to below 500 copies/ml in his analysis.

Quart said that baseline HIV RNA effects durability. If HIV RNA is not suppressed to below detection the effect may not be durable and resistance emerges, and apparently those with higher baseline viral load are less likely to decline to below detection. His analysis was based on data from their protocol 511, including data from both 750 mg tid or 500 mg tid nelfinavir treatment arms who also received AZT+3TC, but excluding the treatment arm receiving AZT+3TC alone.

The definition of a responder is the same stringent one used by Chodakewitz in his analysis: two consecutive values below detection. However, there are some differences between the study populations in Chodakewitz' analysis and in this one. Participants in protocol 511 are naive to all treatments, *and it is important to remember that in this analysis 1,200 copies/ml is the lower limit of detection.* The Chiron bDNA test was used in this analysis. The mean baseline CD4 and viral load of the participants were 288 cells and 153,000 copies/ml.

Study participants with baseline HIV RNA above 100,000 copies/ml had less durable responses than those with lower baseline viral load. Quart reported that study participants with less than 50,000 copies/ml at baseline "had extremely durable response with 95% still responding at one year."

Quart said that he preferred the percent of responders rather than mean RNA response when comparing treatment arms. He said, in study 511 there was little difference between the two dose arms of nelfinavir (750 mg vs 500 mg) when measured by AUCMB and mean change in HIV RNA, but you started to see a statistically significant difference between the two arms when comparing the percent of responders (percent undetectable).

Three ways to look at viral load changes were examined in this analysis: time to response; how to characterize treatment failure (virological - viral load and immunological- CD4); the duration of response. Are baseline CD4 and viral load indicators of duration of response? Is it possible to have a partial durable response?

Quart said, maximal suppression of viral load was reached by a vast majority of study participants by 8 weeks (1,200 copies/ml) although some took longer; 16-20 weeks to reach 500 copies/ml. The time to reach maximal suppression was dependent only on baseline HIV RNA.

Measuring Treatment failure. Quart said, a single HIV RNA test result above the lower limit of detection should not be used as a measure of treatment failure. 28 out of 177 responders on the two nelfinavir doses had a single value above detection, then went down to below detection and remained long-term responders. When they used two measurements above the level of detection to define loss of response, 5 long-term responders were classified as treatment failures although they went back down to below detection and sustained a durable long-term response. However, it is possible that some intercurrent illness or temporary infection caused a temporary rise in viral load.

Dr. Judith Feinberg, an ADAC member from the University of Cincinnati, expressed concern about how to define treatment failure in a study. She finds it common in her experience to see patients below detection for a few months (400 copies/ml in her hospital), and then they may have 420 copies, 500 copies, but then they go back down to below 400 copies. But, we may have to define responders by reaching 50 copies/ml.

Quart said he did not think CD4 changes certainly in the first few months of a study are an appropriate measure of defining whether or not a person is responding to treatment. The CD4 response in study 511 for both the 750 and 500 mg tid nelfinavir treatment arms were about 150 cells at 6 months. Yet, 14 study participants' CD4 count went up some,

came back to baseline and then most of them went back up and continued to have a good CD4 count response. This could be due to biological and/or assay variability. 90% of these individuals had viral load remaining below detection. Generally, Quart said he found good concordance out in time between those who had a durable virological response and an improvement in CD4. A graph shown by Quart indicated that after 48 weeks, for those taking the 750 mg dose of nelfinavir, baseline CD4 did not appear to effect durability of virological response.

Is a Partial virological response possible? The question was raised of whether or not it is possible to lower viral load to a certain level, say 2,000-5,000, and maintain that level for a prolonged period; and, is that approach medically and scientifically sound? Or, is it possible to have a durable partial response?

There are a number of pros and cons to that suggestion, even if it is possible to successfully maintain viral load at a stable low level such as 5,000. Glaxo Wellcome researchers presented data on this subject which is reviewed later in this report. Quart said he did find some study participants that he characterized as having a "new set-point in terms of their RNA." These were patients who had a baseline of greater than 100,000 copies/ml to start with, they were responders, and then they had a relapse. Their HIV RNA was above the limit of detection. It did not go back to baseline but remained stable at about 10,000 copies/ml out to about 36 weeks of follow-up.

If partial suppression can be sustained and replication is still ongoing are mutations and resistance developing? If resistance occurs during partial suppression, you will not want to worsen resistance by continuing the same regimen. This question is addressed by Fred Valentine in the section entitled comments by panelists.

Some researchers say if viral load is at some low level, for example 5,000 to 10,000 copies/ml, viral replication is ongoing and sooner rather than later HIV RNA will rebound as resistance sets in. Generally, once that occurs you may have lost the drugs in the regimen you were using and the immune system will continue to decline. Data reported at the Resistance meeting in St. Petersburg, from the lymph tissue analysis conducted by Joe Wong of UCSD, on a small number of individuals in the indinavir 035 study, suggested that partial suppression of viral activity in the lymph tissue may cause mutations (and resistance) in the lymph tissue to the drugs in the partially suppressive regimen.

HIV RNA below 20 or 50 copies/ml. David Hall, of Boehringer Ingelheim, presented a data analysis of the Incas study where 151 treatment-naive individuals received nevirapine+AZT/ddI, AZT/ddI or nevirapine/AZT. The mean baseline CD4 and viral load were 376 cells and 25,704 copies/ml (4.41 log). CD4 and HIV RNA data for individuals in this study followed out to 72 weeks is available in the current issue of the NATAP newsletter, [NATAP Reports](#). E-mail us with your mailing address for a copy.

Boehringer has stated that compliance was a problem in the Incas study and impacted on the final data. There were 51 study participants initially receiving the triple regimen of nevirapine+AZT/ddI. 20 participants were compliant and 31 were non-compliant. Compliance was defined by having missed a total of 28 days of taking a drug during the

course of the study. Boehringer has stated that 100% of compliant participants receiving the triple regimen reached 20 copies/ml; 80% of compliant individuals taking triple were below 400 copies/ml at one year; and, 70% at 1 year who were taking triple regimen were below 20 copies/ml.

A responder in this analysis was defined as having one measurement below detection. Hall reported that after 4 weeks on study meds 85% (43/51) of the individuals who were responders were below 400 copies/ml; by 8 weeks over 95% were below 400 copies/ml (Roche Amplicor Test). May be these individuals responded more quickly because they were treatment-naive.

As also reported by Chodakewitz in his analysis, lowering viral load to below 50 copies/ml in the Incas study took longer. About 55% of the individuals who ultimately had their viral load lowered (responders) to below 20 copies (Roche Ultra-direct test) were below 20 copies at 8 weeks; by 12 weeks, it was 75% and by 16 weeks it was 90%. But, it took as long as 20-22 weeks for all responders to eventually reach 20 copies/ml. The data show that those with lower viral load at baseline reached below 20 copies considerably more quickly. To measure durability of response by baseline HIV RNA, responders were divided into two groups above and below a median baseline viral load of 4.184 log (about 16,000 copies/ml). This data showed that responders with lower baseline HIV RNA were sharply better able to sustain viral reduction below 20 copies or 400 copies/ml.

The important message from Hall's presentation at this FDA hearing on July 15 was that the analysis of the Incas study data indicated that individuals in this study taking nevirapine/AZT/ddI who did not reach below 20 copies were not able to sustain a response: "confirmed failure to sustain plasma virus below 20 copies/ml is usually associated with return to above 1000 copies/ml....if you got to 20 copies, you were able to sustain a response for up to a year (the last observation point)...but if you did not achieve below 20 copies....your duration of response was on the order of 8 weeks." Those who reached between 20 and 400 copies/ml had the same response with return to baseline as those who did not reach 400 copies/ml.

In the table shown by Hall some individuals who reached 20 copies sustained their response out to as long as 72 or 80 weeks (length of follow-up was limited and variable). Some individuals taking the double therapy AZT/ddI in this study, who went below 20 copies, were also able to sustain it for a prolonged time. Since it is less likely to reach and sustain a reduction to 20 copies with double nucleoside therapy I surmise that these individuals may have had low baseline RNA. In other studies (see AZT/3TC below) only individuals with low baseline HIV RNA have been able to reach undetectable (400 copies/ml) and sustain it for very much of a length of time. The potency of the regimen is a factor in both reaching and sustaining full suppression. In the Incas study about 66% (33/50) of those receiving triple therapy of nevirapine+AZT/ddI were responders- they reached 20 copies. 12 or 13 discontinued therapy prior to reaching 20 copies and about 4 of those 12 or 13 had already reached 100 copies before discontinuing.

It is my observation that if you are able to, monthly monitoring of viral load may be helpful and preferable to less frequent monitoring such as every 3 months. This applies

whether you are using the less sensitive commercial assay which measures to 400 copies/ml (Roche Amplicor) or the 500 copies/ml (Chiron bDNA) or the Roche Ultra-Sensitive Test which measures to 50 copies/ml. The Ultra-sensitive is being more widely used than the Ultra-direct. I believe the more information you have about your response to therapy the better your treatment decision making can be.

If you accept that reaching 50 copies may be necessary to sustain viral load suppression, it will be helpful to observe the pattern of your viral load activity. If you are not reaching 50 copies within a certain period of time you may want to consider modification of therapy with intensification as an option. I would apply this same theory if you are only using the test measuring to 400 or 500 copies/ml. And as mentioned above, it is crucial to give yourself ample opportunity to respond to therapy. Hall reported that a majority of participants in the Incas trial reached 20 copies by 12 weeks, but for some individuals it could take 20-22 weeks. In the Chodakewitz analysis it took some individuals as long as 20-24 weeks to reach 500 copies. Merck measured only as low as 50 copies/ml because they felt at that time that the assay was more precise at 50 copies than at 20 copies/ml, which is the reason I think the ultra-sensitive is preferred to the ultra-direct.

Emilio Emini of Merck Labs said from his experience with participants in study 035 it could take as long as 12 months and sometimes beyond that for some individuals to reach under 50 copies/ml. But, he believes it is necessary to completely shut down viral replication to sustain durability of treatment effect.

How do you balance giving yourself ample time to reach "undetectable" and not waiting too long before considering intensification?

For those reaching 20 copies and who rebounded to above 20 copies, the general pattern was to go back to about baseline within 12-24 weeks. By visual observation of the graphs Hall presented, some individuals' HIV RNA, who had a baseline of about 4.4 log (about 25,000 copies/ml), blipped up and down around 1000 copies/ml. For those with lower RNA at baseline of below 4.4 log, some blipped up and down around 100 copies.

Several researchers I've surveyed suggest that if you detect and confirm a rebounding viral load immediately after its occurrence by close monitoring of viral load it may be preferable to discontinue the protease inhibitor and/or other drugs and switch to a new regimen. If you catch the development of resistance quickly enough you may be able to prevent cross-resistance to the subsequent protease inhibitor or possibly other drugs you can switch to. Optionally, you can use genotypic testing to detect mutations which may have developed for specific drugs in the regimen you are taking; but some experts don't think genotypic testing at this time is reliable enough to use for such decision making; testing methodology varies from lab to lab; some labs only test for certain mutations while another lab tests for all mutations; and interpreting tests results can be tricky. The best test of resistance at this time may be viral load test results.

It appears as though many who reach under 50 or 20 copies/ml may actually be undetectable. That is, they cannot detect any virus in the plasma, which does not necessarily mean there isn't virus because test precision is probably questionable at that level. In the analysis of the Incas study it was found that for some individuals who

reached below 20 copies they could not find any virus (undetectable) while for other individuals who were below 20 copies they found some virus.

The Roche Ultra-Sensitive Assay is not yet FDA approved. Roche is in the process of negotiating with the FDA.

The final industry presentation was by Lynn Smiley and Ralph DeMasi of Glaxo Wellcome. Their analysis was based on 1,076 participants with available HIV RNA measurements in 6 trials and treated with AZT/3TC: CAESAR, NUCA3001, NUCA3002, NUCB3001, NUCB3002 and AVANTI-01. The duration of treatment was 1 year and viral load was measured by Roche Amplicor test with a lower limit of detection of 400 copies/ml.

The analysis frequently looks to draw conclusions based on treatment experience; 48% had less than 6 months prior NRTI experience and 52% had more than 6 months prior NRTI experience. So, there were no truly treatment naive individuals. The overall mean baseline CD4 and HIV RNA were 202 cells and 4.8 log (63,095 copies/ml). 66% of participants had >50,000 copies/ml. At both 6 months and 52 weeks there were between 100 and 200 actual study participants with evaluable HIV RNA values.

The value of this data is limited by the fact that all individuals were taking double-nucleoside therapy. It is not as relevant in today's treatment environment. For example, treatment responses measured by baseline viral load in this analysis were based on individuals taking AZT/3TC. Currently, unless ignorant, no one is merely adding 3TC after prolonged AZT treatment. The data would probably be different if more potent regimens were used, although the general concept that baseline HIV RNA correlates with treatment response probably holds true in most cases. But, I'm not sure baseline HIV RNA correlates with treatment response for sero-converters.

For those individuals with <6 months prior NRTI experience, DeMasi reported a peak viral load reduction from baseline of about 1.9 log at 4 weeks; HIV RNA rebounded to about 1 log below baseline by 20 weeks; at 52 weeks, the reduction from baseline was about 1.2 log. For those individuals with >6 months prior experience, the peak HIV RNA reduction was about 1.3 log at 2 weeks; HIV RNA rebounded at 8 weeks to about .5 log below baseline which was sustained at 52 weeks.

On the first day of the hearing, July 14, much data was presented (see report for day 1) showing that decreases in viral load were correlated with delays in disease progression. Today, four basic topics were addressed by DeMasi: the initial viral load response; the loss of viral load response after having achieved a response; does reaching 400 copies/ml cause a durable response? Can you sustain a partial HIV RNA response? Response was defined by having one test result below 400 copies/ml, and loss of response was defined by two test results above 400 copies/ml.

Initial response to therapy. The hazard ratios presented by DeMasi show that those with lower baseline HIV RNA and <6 months prior NRTI experience are about 4 times more likely to reach 400 copies/ml. They could not detect more than a marginal effect of baseline CD4. Again, for experienced individuals in this analysis only 1 nucleoside, 3TC,

was added to another, AZT. Today merely adding a nucleoside to another nucleoside is not good treatment.

45% of those with <6 months NRTI experience reached a <400 copies/ml. Only 19% of those with >6 months NRTI experience reached <400 copies/ml. Of those who are responders (defined by reaching 400 copies/ml), about 90% of participants reach 400 copies/ml by 12 weeks regardless of prior treatment experience; but, as others have found, it takes as long as 24 weeks for all to reach 400 copies/ml.

About 90% of those with <6 months NRTI experience and baseline HIV RNA <20,000 copies/ml reached <400 copies/ml (undetectable); 68% with 20-50,000, 44% of those with 50-200,000 and only 9% of those >200,000 copies/ml at baseline (>6 months NRTI experience) reached <400 copies/ml. Also, individuals with lower baseline HIV RNA and <6 months NRTI experience tended to reach undetectable more quickly.

But it was much different for those with >6 months prior NRTI experience: 74% with <5,000 baseline copies/ml at baseline reached undetectable (400 copies/ml); 55% with between 5,000-20,000 copies/ml at baseline reached undetectable; 74% and 55%

as opposed to 90% for those with <6 months NRTI experience; 23% of those between 20-50,000, 6% of those between 50-200,000, and no one with >200,000 copies/ml reached undetectable.

At the St. Petersburg Resistance meeting, data was presented (abstract#60) on what appears to be the same group of individuals. After 48 weeks, 72% (range 56-88%) of those who they identified as treatment naive with baseline HIV RNA <5,000 copies/ml, and 42% (range 27-57%) identified as being pre-treated with <5,000 copies/ml were undetectable. It appears as though this analysis was based on the same group of individuals and so naive probably refers to <6 months NRTI experience. However, the results were considerably worse for individuals with higher baseline HIV RNA. Of those with 5-20,000 baseline copies/ml only 32% (naive) and 13% (experienced) were undetectable at 48 weeks; 20,000 to 50,000 - 17% (naive) and 0% (experienced); 50,000 to 200,000 - 14% and 0%; >200,000 - 1% at 36 and 12 weeks respectively (limited follow-up data).

This data indicates that it is more difficult to reach undetectable with double nucleoside therapy compared to using potent triple therapy unless your viral load is low; and, it is more difficult to sustain it if you do reach it.

Loss of initial HIV RNA response for individuals who reached 400 copies/ml.

As with the ability to initially reach 400 copies/ml those with lower baseline viral load and less NRTI experience had more durable responses

At 12, 24 and 52 weeks about 40%, 55% and 65% were no longer below 400 copies/ml. Again, 40% lost their response by 12 weeks. Those with less prior NRTI experience were more likely to have a more durable response. At 12 and 24 weeks there was a difference of about 10% (36% vs 45% at 12 wks, 40% vs 50% at 24 wks) between those with less than or more than 6 months NRTI experience while at 52 weeks the difference was about

5%.

Hall of Boehringer found about 50% loss of initial response at 1 year but the Glaxo data is based on double nucleoside therapy. Also, Boehringer said compliance was a problem in the Incas study.

As observed repeatedly by other research efforts, those with lower baseline viral load have a more durable response to therapy. This is a factor to consider when deciding when to begin therapy and how potent a regimen may be needed. If one's viral load is higher, a more potent regimen may be necessary to reach and sustain 400 or 50 copies/ml. . See forthcoming analysis of ACTG 320 expected to be posted soon to web site.

Does reaching 400 copies/ml mean having a more durable response?

This data analysis showed that for these individuals taking AZT/3TC, if you had <6 months NRTI experience reaching 400 copies/ml indicates a more durable response

(although the durability continually declines) than reaching 400-1,000 or 1,000-5,000. There was a slight difference in durability between reaching 400-1,000 and 1,000-5,000. For those with >6 months NRTI experience there was no difference in durability whether you reached 400, 400-1,000, or 1,000 to 5,000 copies/ml. This appears to be generally applicable, as stated earlier, the nadir of viral load response correlates with durability.

Can you partially suppress viral load? This was an analysis of how many individuals who rebounded above 400 copies/ml could keep their viral load "stable." Stable was defined as <5,000 copies/ml. The analysis was restricted to study participants who had baseline viral load no more than .5 log above 5,000 HIV RNA. 5,000 plus .5 log equals about 15,000 copies/ml. This appears to me to be very significant to the analysis because 15,000 is a low viral load to begin with and is not far apart from 5,000. They concluded that at 24 weeks about 60% of those with <6 months NRTI experience and about 48% of those with >6 months NRTI experience remained stable. At 44 weeks, about 40% of those with >6 months NRTI experience remained <5,000, and about 50% of those with <6 months NRTI experience remained below 5,000. Which means 50-60% were not below 5,000 copies at 44 weeks.

The data does not reflect upon the ability to retain a partial suppression if your baseline viral load is above 15,000 copies/ml.

FDA Summary

Michael Elashoff, PhD, of the FDA summarized the data. He said the FDA is focusing on time to loss of response as the primary response in these studies. This endpoint may also include clinical and CD4 endpoints. The initial phase of an HIV RNA trial could be used for accelerated approval on the basis of percent of response and the long-term follow-up would address the durability.

Elashoff identified the following issues -

1. what is a response

2. a loss of a response
3. how long should subjects be kept on initial therapy while waiting for a response
4. how long should trials be
5. how do different populations effect these issues

Elashoff mentioned 3 phases of HIV RNA during the studies discussed in today's hearing: the initial decline to some low level, be it 20, 50, 400, or 1,200 copies/ml; the time spent at or near (partial suppression) that low level; and the increase.

For the initial response to therapy:

1. Agouron found about 8 weeks was necessary to reach 1,200 copies/ml
2. Beohringer said 8 weeks was adequate to reach 400 copies/ml
3. using 2 nucleosides, Glaxo found 12 weeks captured most responders
4. Merck's data included indinavir monotherapy, those receiving indinavir+AZT/3TC in 035, and individuals taking AZT+indinavir; but, most of the combination therapy were of individuals taking indinavir+AZT. Merck found 12-16 weeks captured most responders to 500 copies/ml.
5. to reach 20 copies/ml, Boehringer reported 20-22 weeks; Merck reported about 28 weeks to capture those reaching 50 copies/ml.

Some individuals, however, can take longer to reach the lower limit of the different assays. It is not just those with higher baseline HIV RNA who may take longer to reach "undetectable." Elashoff mentioned that data from companies doing presentations today show that some individuals with lower baseline HIV RNA can take longer to reach "undetectable." Although there is a downward trend in RNA there are bumps along the way. Therefore, subjects should not be classified as early failures if their HIV RNA is detectable but not increasing.

Differences in time to reach undetectable were found based on differences in baseline viral load and CD4. Those differences varied from 4 to 6 to 8 weeks depending on the differences in baseline viral load. Not all of the analyses found that there were differences based on baseline CD4 values. Generally, those with higher baseline RNA take longer to reach undetectable.

As mentioned earlier in the report, Beohringer reported that some study participants who reached 50 copies had some quantifiable virus (20 or 30 copies, etc.) while for others below 20 they couldn't find any virus. It may be too soon to implement the following idea but it's worth mentioning. Beverly Dale, of Roche Molecular Systems, addressed the committee in the open session and suggested three interesting patient groups that could be studied: those that are quantifiable above 50 copies/ml, those that are not quantifiable (below 50 copies) but actually get a virological titer (some virus is found--10, 20, or 30 copies), and the third group are those for which they can't find any virus. Roche is in the

process of negotiating with the FDA about approval of their Ultra-Sensitive Test (50 copies/ml).

Highlights from comments by David Feigal, outgoing director of the FDA antiviral drug division

It is presumptuous for us to predict more than a couple of years at a time in this business. But, how are we going to use viral load and CD4 counts in our trials? Much of early HIV treatment was empiric therapy (treatment decision making by doctors based only on experience and observation). Due in part to the advent of viral load testing and the many new treatments, it is no longer satisfactory to treat HIV empirically on fixed regimens without individualizing therapy.

In individualizing therapy we can look at a person's initial response compared to what may be detected in clinical studies. We can then look at the time to loss of response, and the people who have no response; we need to look at durability and try to evaluate the cause of the loss of response.

Some of the causes for loss of response include: resistance, drug interactions, poor absorption.

There are responses worth having that may not be optimal, but are associated with survival benefits.

We need to get a good estimate of the magnitude of response across a spectrum of patients: pre-treated and naive, high and low viral load.

From a regulatory standpoint, what we are looking at is moving away from a label which simply says this agent is approved to treat HIV infection to a label that would describe the performance characteristics of the product: how long to wait for a response, what is the magnitude of response, how long the response might last; this information can help individualize therapy to baseline viral load levels; and what kinds of things need to be done to evaluate what to do when the response is lost.

We need to collect response to therapy measured by both viral load and clinical endpoints.

What is sub-optimal therapy? Optimal therapy is not a simple phrase, because this is a disease that needs to be treated for a long period of time. What is optimal in the short term may not be optimal in the long-term, and we need to be able to study the tradeoffs of saving agents with simpler regimens versus maximal therapy, and even though various advisory groups (draft PHS Guidelines, IAS guidelines) have taken positions in one direction and the other, in my mind at least, these are still open questions. We want to create incentives in drug development to find agents that have the longest durable response as possible and that preserve the maximal therapeutic options.

Comments by panelists

One of the two guest statisticians on the panel, Joel Verter, cautioned that reliance only

on surrogate markers can be misleading. The other guest statistician, Vernon Chinchilli, said, given the consistency of the results across a variety of data sets.....I am pretty well convinced that the way to go is to look at viral load. Scott Hammer, Judy Feinberg, Fred Valentine, Pamela Diaz, Wafaa El-Sadr, HIV treaters and researchers, as well as the community rep Mark Harrington, expressed support that viral load is an appropriate measure of disease activity. But they all had a variety of concerns including: long term safety and efficacy; why some individuals are non-responders; there is evidence that viral load is a predictor of clinical benefit but an incomplete predictor; why are some individual's viral load still detectable after 24 weeks; Verter expressed concern that the studies presented had discontinuations or dropouts and that changes the data; Hammer said, changes in 4 to 24 weeks after starting therapy are strongly associated with improvement in clinical benefit, but we still have precious little data beyond that in time, although it is reasonable and logical to conclude that more durable suppression beyond that point will lead to further clinical benefit; treatment induced toxicities is a concern; what events will trigger changes in therapy, and the development of clinical events should be tracked.

Partial suppression. Valentine said, I think our goal should be suppression of viral replication to under 50 copies for as long as possible for those who are being treated to avoid selecting for resistance and avoid making these drugs not useful for the patient... But he added that for somebody with established disease whose cruising along on no therapy with 1,000 or 2,000 copies I would follow them closely without therapy.

For those individuals who were described as reaching partial suppression in some of the data presented, it is suggested that their virus is wild type, not resistant virus. If it were resistant virus, you would expect that it would rush forth considerably, to higher levels unless it were very much compromised in its ability to replicate; so it could be that this virus represents an emerging pool from provirus, which is wild-type, which would be restrained, but not eliminated perhaps because some stimulus is making it come forth.

Hammer said if accelerated approval decisions will be based on 16 to 24 weeks, 48 weeks is an absolute minimum.

There was discussion about measures of a loss of response including CD4 count going down, development of a clinical event, and a variety of different quantifications of confirmed rebounds of viral load from nadir. There was considerable concern about being able to factor in all these questions particularly when dealing with populations at varying stages of disease. For example, individuals entering trials with low CD4 counts may have certain OIs unmasked fairly quickly after therapy begins.

Finally, I suggested at the hearing that the FDA require that a new drug establish superiority to existing treatments and that contributed to using double nucleoside treatment arms in studies. Jeff Murray, of the FDA, responded and said that is not true, that the FDA accepts equivalence studies and there was at least one example of an equivalence study leading to approval.