

[National AIDS Treatment Advocacy Project](#)

Report From FDA Hearing on Using Viral Load as an Endpoint

by Jules Levin from Silver Springs, MD - July 14, 1997

Today was the first day of a two day public hearing before the Antiviral Drug Advisory Committee arranged by the FDA; for the purpose of addressing whether or not plasma (blood) viral load can be used as a primary endpoint in judging the efficacy of a drug for full approval as well as for accelerated approval. The main question is: can viral load be used as an endpoint rather than disease progression itself to decide full approval for a new drug? This hearing was very well attended on this first day, I estimate that 200 people were in attendance, as the changes in clinical studies proposed by using viral load as an endpoint can have a significant effect on HIV clinical trials.

Up until now a new drug is judged for full approval by whether or not it delays disease progression and death. If viral load were used as a primary endpoint instead of disease progression, the criteria for approval might include: how much reduction in viral load occurs, how low can viral load be reduced (for example, 20 copies/ml, or 400 copies/ml), percentage of study subjects reduced to undetectable, and duration of effect. However, the FDA is proposing that using viral load as an endpoint would be an option. Drug companies could still conduct a clinical endpoint study using disease progression. It is possible, if this proposed change is approved, that a company could conduct both types of studies, using viral load endpoint studies for full approval followed by a new type of clinical endpoint study in post approval. Treatment strategy trials have been suggested as a format for conducting a clinical endpoint study.

Changes in viral load due to therapy predicts disease progression. 10 to 15 studies were reviewed by a series of about 10 speakers who presented data essentially all supporting that reductions in viral load in plasma due to treatment correlates with HIV disease progression. About one year ago Dr. David Feigal, Director of the Office of Drug Evaluation at the FDA, told me that viral load needed to be validated and today he said to the open hearing that it has been validated. Progress is being made, although slowly.

It was pointed out today that there are some limitations to viral load testing. For some individuals their viral load can decline while their CD4 declines. There can be variabilities that confound reproducibility; for example, one lab's results can be more reliable than another lab. Improper specimen handling can occur at a number of different points where different individuals handle a specimen. Other sources for variation of test results can include: individual biological fluctuation, inter kit variability (Roche vs bDNA), intra kit variability (among kit lots), intra assay variability (among replicates in a batch), inter assay variability (among replicates in different batches).

You can totally ignore the previous paragraph if it is too technical; because nonetheless,

the data presented today from many studies indicates that viral load changes due to treatment effect predicts disease progression regardless of these limitations. It is important to remember that one test result should be confirmed with a second test result before making a treatment decision because a single test result may not accurately reflect viral load. It is also important to probably use the same lab because when switching from one lab to another, methodology and quality assurance may differ. It is important to stick to the same test (Roche Amplicor PCR or bDNA) when comparing results because values from one test do not correlate with the values of the other test.

In ACTG 175, there was a 90% reduction in the risk of progression associated with a 1 log reduction in viral load between baseline and week 56.

Ira Marchner, PhD statistician at Harvard School of Public Health and the ACTG, reported on a retrospective (look back) analysis of over 1,000 individuals studied over 24 weeks in 8 trials (ACTG 116A, 116B, 117, 175, 197, 229, 241, 250) where the drugs studied were ddI, ddC, nevirapine and saquinavir. The Roche PCR test was used, baseline CD4 and viral load were 200 cells and 50,000 copies/ml, the follow-up was 1 year, and mono, double and triple therapy were utilized. He concluded that the collective data indicates that the amount of change in HIV RNA correlates proportionally with disease progression; larger reductions in viral load reduce disease progression more than smaller reductions in viral load; but smaller reductions also reduce disease progression. He said baseline HIV RNA and changes due to treatment both independently predict disease progression.

Ralph DeMasi and Lynn Smiley of Glaxo Wellcome showed data indicating that the durability of suppression of viral load <5,000 copies/ml correlates with delayed disease progression. They also said that the amount of suppression correlates with disease progression; that is, a 2 log reduction delays disease progression more than a 1 log reduction. And, they said a higher baseline viral load correlates with more rapid disease progression. They also showed data indicating that lowering viral load to <400 copies slowed disease progression more than lowering viral load to between 400 and 5,000 copies; while that was superior to only lowering viral load to between 5,000 and 20,000.

Several speakers showed data indicating that the amount of change in viral load is proportional to the number of events of disease progression. In other words, an individual who achieves a 2 log reduction in viral load is less likely to develop an HIV related opportunistic infection or disease progression than someone who achieves a 1 log reduction.

Christy Chuang-Stein, Director of Clinical Development Biostatistics at Pharmacia and Upjohn, presented data on over 2,000 individuals in delavirdine studies 0017 and 0021. She showed baseline HIV RNA as well as baseline CD4 correlated with disease progression. She said in her study that a 1 log reduction in the first 12 weeks reduced progression by 57%.

Baseline viral load predicts disease progression. Several speakers showed data indicating that baseline viral load predicts disease progression. The higher your baseline viral load the more rapidly you should progress.

The lower your baseline viral load the lower you may be able to suppress viral load. So, individuals with higher baseline viral load and/or lower CD4 may need more potent therapy to achieve the same level of suppression as an individual with a lower viral load and/or higher CD4 count. This point was made at the St. Petersburg Resistance meeting on June 25, 1997. These are factors in deciding when to begin therapy. It is easier to achieve "full suppression" of viral load when your baseline HIV RNA is lower. A lower baseline RNA may also indicate a more intact immune system; of course, the CD4 count is also a factor in judging the competency of your immune system.

At St. Petersburg, the virological data from ACTG 320 was previewed. In this study the baseline CD4 was about 80-85 cells and the baseline HIV RNA was about 100,000 copies/ml (5 log). For those individuals receiving the triple regimen of indinavir+AZT (or d4T)+3TC, after 40 weeks only 40% were still undetectable (<500 copies/ml) in the group with <50 CD4 at baseline. In the group with 50-200 CD4 at baseline, who received the same triple regimen, 70% remained undetectable at 40 weeks. This differs from the results of Merck's study #035 where the baseline CD4 and viral load were 152 cells and about 40,000 HIV RNA. Although the number of evaluable study participants is considerably less in 035, after 68 weeks about 80-85% remained undetectable.

On the basis of these results and other studies a number of leading researchers concluded at the St. Petersburg meeting that more potent therapy than was used in these two studies may be needed for individuals with more advanced HIV; that is, individuals with lower CD4 and/or higher viral load. In fact, participants in both 320 and 035 were or could be AZT experienced and only naive to indinavir and 3TC, so they received only two new drugs. Individuals with more advanced HIV may need 3, 4 or possibly 5 new drugs to achieve adequate and durable suppression of viral load.

Another important point related to viral load that was prominently discussed both in St. Petersburg and at this FDA hearing is that the nadir of suppression correlates with durability. The more you lower viral load the more durable the effect should be. Lowering viral load to below detection (400 or 500 copies/ml) correlates with durability of effect. In fact, although there is no data yet supporting this notion, a number of experts feel that the best durability will be achieved by lowering viral load below 20 copies/ml. It is expected that an application for approval for the Roche Ultra Sensitive viral load test is being submitted to the FDA this month.

Plasma viral load and lymph tissue viral load. William Cavert, MD of the Dept of Microbiology at the University of Minnesota, discussed this subject. He said, >99% of total body virus resides in the lymph tissue. There are two main compartments: FDCs, follicular dendritic cells and mononuclear cells (MNC). Lymph tissue sites used for monitoring viral load can be lymph nodes, tonsils, spleen and gut associated lymph tissue (colon).

There are a number of concerns or potential limitations about the ability to accurately access viral load in the lymph tissue. When you take a sample of tissue you don't know if that piece of tissue accurately reflects how much virus is in all the lymph tissue. For example, you may have sliced a sample that doesn't contain virus or contains less virus while tissue just adjacent that wasn't sampled may have more virus. Another concern is,

is the assay being used sensitive enough? He raised several other limitations of current testing methodologies.

He listed a number of studies which showed no correlation between plasma and lymph tissue viral load. He surmised that the therapies used in these studies may have been too weak to cause reductions in lymph tissue viral load. He went on to cite two more recent studies-- Marianne Harris, Vancouver 1996 (reviewed on NATAP web site) and Ashley Haase, Science 1997 (also reviewed on NATAP web site in Birmingham Reports). Both of these studies used potent therapies and indicated a correlation between plasma and lymph tissue viral load reductions. The Harris study was of naive individuals taking nevirapine/AZT/ddI in study #1046; the Haase data comes from an analysis of naive individuals taking ritonavir/AZT/3TC which was presented at Birmingham. In both studies a significant percentage of participants rendered their viral load to undetectable. This correlated with a significant reduction in viral load in the lymph tissue sample by the respective investigators.

Cavert showed that in the individuals receiving the ritonavir therapy there was significant reduction in viral load in both lymph tissue compartments-- FDCs and MNCs. He surmised that when you shut off production in the MNCs you shut off production in the FDCs and plasma.

He said that in a paper by Sei in 1994 there was a rough correlation between lymph tissue DNA and plasma RNA. But based on a paper recently published and presented in St. Petersburg by Robert Siliciano of the NIH, Cavert said this question may remain open. In St. Petersburg, Siliciano indicated that post integrated proviral DNA may be a virus reservoir that takes a long time to decay (5-7 months). David Ho and Marty Markowitz have identified two phases of viral decay-- actively reproducing cells and latently infected cells. This proviral DNA may be a third phase of decay not accounted for by Ho in his estimates that it could take 3 years to eradicate the virus. There still are questions and doubts about Siliciano's data but it will have to be reckoned with. In St. Petersburg some researchers were speculating that the three years could be extended several more years if the Siliciano data holds up. But several other factors to consider were suggested that might rebut Siliciano's conclusions including that once you reduce virus low enough the revitalized immune system might kick in and protect against what may be only a very small amount of virus in the compartment described by Siliciano.

Cavert said that in sero-converters plasma viral load may be higher than in lymph tissue. To me this may mean that eradication may be more possible for that group than after virus has a chance to set up house in the lymph tissue. He also said that in late stage disease lymph tissue may be destroyed and virus may mostly reside in the blood.

Sub-optimal therapy causing a viral load reduction in plasma may not correlate with a like reduction in lymph tissue. This may be an important point made by Cavert because in St. Petersburg it was concluded from the Joe Wong lymph tissue study of subjects in the 035 study of indinavir, that partial suppression in the lymph tissue may be worse than no suppression. A regimen that is only partially suppressive in plasma may be worse for viral load in lymph tissue than no suppression at all. This is important as it relates to the use of double-nucleoside therapy. Double-nucleoside therapy may only

achieve partial suppression of virus in plasma, which may not be beneficial to viral load in the lymph tissue. Many doubts have been raised about using double-nucleoside therapy as it is generally accepted that the goal of therapy should be to lower viral load to undetectable, if possible; but double-nucleoside therapy is not likely to achieve that goal and if it does it is less likely to sustain it than a more potent regimen.

This raises the issue of the ethics of using double-nucleoside therapy in clinical trials. The FDA has said, in the recent past, that they cannot tell study designers which comparison arms to use and therefore they cannot forbid the use of double-nucleoside therapy. Drug companies continue to use double-nucleoside comparison arms in studies. In fact at this point in time the FDA requires that a new drug display it is superior to currently available therapies to gain approval thereby in fact encouraging or requiring the use of double-nucleoside comparison arms. This concern is even more acute considering that the new PHS/NIH Treatment Guidelines recommend the goal of therapy should be to reduce viral load to undetectable with a potent regimen consisting of a potent protease inhibitor combined with two nucleosides.

I plan to raise this issue at tomorrow's hearing when I go to speak at the microphone.

The FDA concluded at the end of the day that:

- the absolute level of viral load was more important than the amount of the reduction
- the lower the HIV RNA the more reduction in risk occurs
- the longer that viral load stays low the better

Tomorrow's scheduled speakers include Jeff Chodakewitz MD from Merck, Barry Quart PharmD with Agouron, David Hall PhD with Boehringer Ingelheim, and Lynn Smiley and Ralph DeMasi of Glaxo Wellcome. As well, the committee will discuss the presentations and the issue and then deliver an opinion on using viral load as an endpoint. As is the case with all ADAC recommendations, the FDA is not required to follow ADAC recommendations but usually follows them and sometimes the FDA attempts to coax the committee to an opinion they prefer.