

National AIDS Treatment Advocacy Project

FDA Proposal For Using Viral Load In AIDS Clinical Studies

May 22, 1997

On May 16th at the FDA, officials from the agency hosted a small meeting for community advocates where they previewed an outline of their tentative plans for changing the design of AIDS clinical studies. Currently, to receive accelerated approval, a new AIDS drug is judged by its effect on changes in CD4 and viral load. To receive full approval a new drug must prove that it delays disease progression and improves survival.

To gain full approval under the current system, a new drug in combination with currently accepted therapy is compared to the current therapy without the new drug (for example, ACTG 320 compared indinavir+AZT+3TC vs AZT+3TC). If more study participants develop clinical endpoints (HIV related opportunistic infections or illnesses and death) in the treatment group receiving the current therapy as compared to the therapy with the new drug then the new drug receives full approval.

A number of studies have established that changes in viral load due to therapy correlate with or predict disease progression and survival. As well, it may not be possible any longer to recruit participants for those traditional types of studies. In today's treatment environment, a person may not be willing to enter a study that risks blinded randomization to a therapy inferior to what he or she may need. With the availability of viral load testing and therapies proven to delay progression and death, it is believed by many that it may be of questionable necessity and unethical to ask study participants to make that sacrifice. Still, some maintain that clinical endpoint studies are the best way to characterize a drug's efficacy and safety, although they may doubt the feasibility of conducting such studies.

Many community advocates and others thought that ACTG 320, which began around January 1996, was unnecessary and unethical. They thought it was already adequately established that a potent protease containing triple therapy regimen was superior to double nucleoside therapy in delaying disease progression and death for the group of individual's studied in 320, those with CD4 below 200. The FDA and other researchers thought the evidence was not yet clear and convincing and they said the study could be enrolled and completed. The study was stopped early and there was some trouble with enrollment. An inordinate number of minorities enrolled in the study, the pace of enrollment slowed, and a number of participants dropped out either because they wanted

access to better therapy (Crixivan was approved and available in the pharmacy) or because their viral load was dropping. Still, some continue to maintain that clinical endpoint studies are the best way to characterize a drug's efficacy and safety, although they may doubt the feasibility of conducting such studies.

At this May 16th meeting, the FDA discussed their proposal to address these concerns.

The FDA proposed that the criteria for a new drug seeking approval should include what percentage of study participants are "undetectable", and how durable is this effect.

Currently, the most successful potent multi-drug therapies are able to suppress viral load below detection in about 80-90% of study participants. A new drug containing regimen will be measured against this level of success or should have other redeeming qualities including: preferable dosing regimen (once or twice per day), favorable side effect profile, favorable resistance or cross-resistance profile. These potential qualities will be factored into review of a new drug along with its effect on viral load. If studies of a new drug indicate less than 80-85% undetectable, it will not be precluded from accelerated approval but labeling may reflect such study results.

Accelerated approval will be kept in place but the percent below detectability will be a new criteria for consideration of receiving accelerated approval. For full approval, the FDA is suggesting to measure the new drug by how durable the effect is, that is how many remain undetectable and for how long.

Labeling of approved drugs will probably have to be adjusted to reflect these changes in criteria.

The FDA said they cannot mandate to a drug company or researcher what comparison or control arm should be used in a study. According to the current FDA proposal, that decision and its review will be left to study designers, the local IRB and community advocates. Therefore, there remains a danger that a sub-optimal treatment arm can still be used in a study. Although many believe we should strive for a situation where no study participants risks randomization to a treatment arm not adequate for their individual needs, the FDA says we don't yet know enough about which therapy is adequate, and that at any rate safeguards regarding sub-optimal therapy should be left to local IRBs.

The FDA proposal, as it is currently constructed, does not mandate that a drug company must use the new viral load goals in their clinical endpoint studies. They will have the option of using viral load as an endpoint or using the traditional clinical endpoint study.

If these new proposals are accepted when will they be implemented? Critical

pre-accelerated approval studies for several important drugs are about to begin: DMP-266, 141W94, 1592U89, PMEA. The FDA proposal and related issues will be addressed at a public meeting in July with the Antiviral Drug Advisory Committee, at which other interested parties from industry, academia and the community will probably be present.