

National AIDS Treatment Advocacy Project

ACTG 320, the controversial clinical endpoint study of Crixivan, has been stopped due to convincing data demonstrating clinical superiority

from Jules Levin

The Data and Safety Monitoring Board of the ACTG reviewed interim data and recommended closure of the study due to "demonstration in this study of clinical superiority" of indinavir/AZT(or d4T)/3TC over the comparison arm of AZT(or d4T)/3TC.

The overall length of follow-up of participants for both treatment arms was 38 weeks. The data was stratified by over or below 50 CD4. 1146 individuals started the study which was designed to study those with <200 CD4. Participants were protease inhibitor naive with no more than 7 days prior 3TC experience (in effect 3TC naive). Those who were intolerant to AZT were permitted to take d4T instead, although most took AZT.

Following is some of the data released by the ACTG. A more extensive report will follow on this web site

A total of 579 were randomized to receive AZT (or d4T) + 3TC; 577 were randomized to receive indinavir = AZT (or d4T) + 3TC.

Overall, of those randomized to AZT/d4T+3TC, 63 subjects (11%) progressed to a first clinical AIDS-defining event of AIDS or death, and 18 (3%) progressed to death. Of those randomized to the triple regimen including indinavir, 33 (6%) progressed to a first clinical event or AIDS, and 8 (1.3%) progressed to death.

Baseline CD4 < 50: For those who entered the study with < 50 CD4 and who were randomized to the double nucleoside treatment arm (n=220), 44 (20%) progressed to a first clinical event of AIDS or death; and 13 (5.9%) progressed to death. For those in the triple drug arm (n=219), 23 (11%) progressed to a first AIDS event or death and 5 (2.2%) progressed to death.

Baseline CD4 > 50: For those who entered study with >50 CD4 (50-200), and randomized to the double nucleoside arm (n=359), 19 (5%) progressed to a first clinical/AIDS event or death, and 5 (1.3%) progressed to death; for those receiving triple combination including indinavir, 10 (3%) progressed to first AIDS event or death, while 3 (0.8%) progressed to death.

Investigators declared that the study demonstrated the clear clinical superiority of the triple therapies used in this study over the double nucleoside therapies. The overall reduction in progression to AIDS of 11% to 6% reflected a 50% reduction in hazard and was statistically significant ($p=0.001$). The reduction rate of disease progression in the < 50 CD4 group was from 20% to 11% from the double to triple regimens ($p=0.005$). CD4 and plasma HIV RNA analysis are expected to be available in the near future as they are being prepared.

Investigators characterized the study medications as being well tolerated.

COMMENTARY: As many of you know, the conduct of this study was controversial. Many community advocates and some researchers opposed conducting this study, but the FDA and some researchers insisted it be conducted because of FDA regulations and for "scientific purposes". Maybe, these study results in conjunction with other data will spur the FDA to consider using viral load as an endpoint rather than conducting these types of studies where people have to get sick and die to prove a point that appears to have been proven already. As it turned out there was a 28% dropout rate in the double nucleoside arm

versus 11% in the indinavir arm. Most of the 50% of the premature withdrawals were because subjects wanted open-label protease inhibitor therapy and/or were concerned about a high viral load. This occurrence probably would tend to narrow the differences in progression rates between the two study arms. Traditional clinical endpoint studies are increasingly difficult to implement any way, so an alternative approach needs to be designed.