

National AIDS Treatment Advocacy Project

NEVIRAPINE Update--safety and efficacy data, discussion of dangers of interaction with protease inhibitors, considerations of how to use the drug -- 9/14/96

Prior to Vancouver in July '96, nevirapine received accelerated approval for marketing from the FDA. A comprehensive [report of the data](#) and other information presented at the FDA hearing is available on the NATAP web-site. I suggest you read that article for a fuller perspective of nevirapine, and its safety and efficacy data and how to use it.

In Vancouver, an update to the data was presented. Prior to Vancouver only 28 weeks of viral load data was available for the important BI study #1046. This article reports 52 weeks of viral load data, which was presented in Vancouver. The 1046 study examines treatment of drug-naive individuals with the triple therapy of AZT/ddI and nevirapine vs. nevirapine/AZT vs. AZT/ddI.

First, a warning---nevirapine is processed through the same drug processing system in your liver (cytochrome p450) as are protease inhibitors--saquinavir, ritonavir, indinavir and nelfinavir. As a result, drug interactions can occur if you take nevirapine with any of these protease inhibitors or any other drug(s) that are also processed through the same system. Combining nevirapine (or delavirdine--both drugs are in the same class, non-nucleoside reverse transcriptase inhibitors--NNRTI) can cause alterations in the drug levels of the protease inhibitor and/or nevirapine. It is strongly recommended that is preferable to wait for the results of the drug interaction studies that are now being conducted by the manufacturer before combining nevirapine with a protease inhibitor.

Nevirapine + AZT/ddI

baseline characteristics

mean CD4--387

mean HIV RNA-- 17,498

51 subjects were randomized to this treatment arm treatment-naive 98% were asymptomatic

previously available data (estimated)

1. mean HIV RNA reduction from baseline at 28 weeks-- 1.65 log (n=27)
2. mean CD4 increase from baseline at 28 weeks-- 120 cells (n=36)
3. percent of subjects below limit of detection (undetectable--200 copies/ml)--73%

(RNA reductions may have been more but for the facts that the Roche Amplicor viral load test has as its lowest limit of measure 200 copies/ml and the baseline mean RNA value was low)

New data (estimated)

1. mean HIV RNA reduction from baseline at 52 weeks-- 1.40 log (n=34)
2. mean CD4 increase from baseline at 52 weeks-- 140 cells (n=34)
3. percent of subjects below limit of detection (200 copies/ml)-- 60%

Commentary--As you can see, the percent of study subjects below the level of detection is reduced from 73% at 28 weeks to 60% at 52 weeks. As well, the HIV RNA reduction at 52 weeks is not quite as low as it was at 28 weeks.

Compliance with taking the assigned treatment regimen appears to have affected the data results. 24 individuals taking the nevirapine/AZT/ddI were defined as compliant and their mean RNA reduction from baseline was about 1.65 log at the week 40-52 average. 16 individuals were defined as not compliant and their mean RNA reduction was about 0.80 log.

There appears to be a correlation in this treatment arm between an individual's baseline HIV RNA value and whether or not their viral load is undetectable (below 200 copies/ml) after 40-52 weeks of therapy. About 82% with less than 10,000 RNA copies/ml at baseline, who received triple therapy, remained undetectable after 40-52 weeks of therapy; about 50% remained undetectable if their baseline RNA was between 10,000 to 28,184; about 20% remained undetectable if their baseline RNA was between 28,184 to 63,095; and, for those with greater than 63,095 about 20% remained undetectable. --(*end of commentary*)

AZT + ddI

baseline characteristics

mean CD4-- 392 cells

mean HIV RNA-- 28,708 copies/ml

51 subjects randomized to this treatment arm treatment-naive 96% asymptomatic

previously available data (estimated)

1. mean RNA reduction from baseline at 28 weeks-- 1.30 log (n=27)
2. mean CD4 increase from baseline at 28 weeks-- 70 cells (n=38)
3. percent below the limit of detection (200 copies/ml)-- 45%

New data (estimated)

1. mean RNA reduction from baseline at 52 weeks-- 0.90 log (n=31)
2. mean CD4 increase from baseline at 52 weeks-- 30 cells
3. percent below the limit of detection (200 copies/ml)-- 30%

Compliance appears to affect these data results: the 27 individuals defined as compliant with the assigned regimen of AZT/ddI had a mean reduction in viral load from baseline of about 1.20 log. The 8 individuals defined as not compliant had a mean reduction in viral

load from baseline of about 0.30 log.

AZT + Nevirapine

baseline characteristics

mean CD4-- 346 cells

mean HIV RNA-- 35,156 copies/ml

47 subjects randomized to this treatment arm treatment-naive 96% asymptomatic

previously available data (estimated)

1. mean RNA reduction from baseline at 28 weeks-- 0.40 log (n=21)
2. mean CD4 increase from baseline at 28 weeks-- 10 cells (n=30)
3. percent below the limit of detection (200 copies/ml)-- 0%

New data (estimated)

1. mean RNA reduction from baseline at 52 weeks-- 0.25 log (n=23)
2. mean CD4 increase from baseline at 52 weeks-- 0 cells (n=24)
3. percent below the limit of detection (200 copies/ml)-- 0%

Compliance also affected this group in the same way: the 22 individuals defined as compliant with taking nevirapine/AZT had a mean RNA reduction from baseline of about 0.30, while the 6 defined as not compliant had a mean increase in viral load.

Safety-- The main safety concern with taking nevirapine is the development of a rash. Following is safety data for the first 6 months of the 1046 study. (NVP=nevirapine)

	NVP+AZT+ddI (n=51)	NVP+AZT (n=47)	AZT+ddI (n=53)
patients with Rash	14 (28%)	15 (32%)	7 (13%)
SEVERITY			
Mild	11	9	7

Moderate	1	4	0
Severe	2	2	0
SJS*	0	0	0
POSSIBLE RELATIONSHIP			
Yes	12	11	3
No	2	4	4
Patients Discontinued Due To Rash	3	4	0
*Stevens-Johnson Syndrome			

Commentary--Nevirapine has been in clinical research studies for a prolonged period of time. It was difficult to figure out an effective way in which to use the drug. In the previous NATAP web-site article reviewing nevirapine, data from study #'s 241 and 1037 are reported; those two studies explored nevirapine therapy in combination with 1 or 2 two other nucleosides in individuals with previous drug experience of either AZT alone or multiple nucleoside experience. The benefits to the study participants were limited, and much inferior to the benefits achieved by those treatment-naive individuals in study #1046 who received triple therapy of nevirapine/AZT/ddI. As well, even the treatment-naive individuals in 1046 who received treatment with AZT/nevirapine received limited benefit. Apparently, the development of resistance prevents sustaining of benefits. At the FDA hearing in June for nevirapine, it was well recognized by the Advisory Committee panel that the optimal success of nevirapine therapy would be in a potent regimen of drugs. Nevirapine along with 1 additional nucleoside is very limited in its amount of suppression upon viral replication, for both treatment-experienced and -naive individuals.

The question remaining is how can we best utilize nevirapine and other NNRTIs in development (e.g. delavirdine and DMP-266) in the context of protease inhibitor therapy?

For treatment-naive individuals, one option is to consider, for initial therapy, a three-drug regimen of 2 nucleosides with nevirapine (for example, nevirapine with AZT/ddI, AZT/3TC or d4T/ddI); and when efficacy may diminish, the individual could transition into a protease inhibitor regimen.

Two important elements in these considerations are the possibility of combining nevirapine (or another NNRTI) with a protease inhibitor and the development of cross-resistance between NNRTIs. The manufacturer of nevirapine, Boehringer Ingelheim, and the manufacturer of delavirdine, Pharmacia & Upjohn, have only recently begun to conduct drug interaction studies between their drugs and protease inhibitors. Both companies and the FDA have been wrong in not having conducted these studies considerably sooner.

An option for both treatment-naive and experienced individuals is the combination of both a protease inhibitor and an NNRTI in the same regimen. Upon initiation of taking nevirapine, it is a potent drug that can attain a 1.75 log reduction in HIV RNA within the first few weeks of therapy. The problem with nevirapine is that, when used as monotherapy or in a sub-optimal regimen -- that is, one that does not achieve potent viral suppression -- resistance with nevirapine sets in very quickly and the viral load reduction can rebound quickly and significantly. In study #1046, those treatment-naive individuals randomized to triple therapy achieved significant viral load reductions and CD4 increases which were sustained, but individuals in the AZT/nevirapine treatment arm mostly did not sustain benefits; those receiving AZT/nevirapine experienced a mean initial peak viral load reduction of about 1.75 log and a mean initial peak CD4 increase of about 80 cells within the first few weeks, but the benefits relatively abruptly declined; by 16 weeks of treatment, the mean CD4 increase declined to about 25 cells and the mean viral load reduction was only 0.60 log from baseline; at 28 weeks, the mean CD4 increase from baseline was about 10 and the mean viral load reduction was about 0.40 log.

The implication is that the rendering of viral load, by the triple drug combination of nevirapine/AZT/ddI in treatment-naive individuals, to such low levels as achieved in this study, sufficiently halts HIV replication and thereby mutation (that is, resistance). That seems to be the reason that benefits are sustained. So, the addition of nevirapine to a protease inhibitor regimen might accomplish the same result. For those individuals who have exhausted other drugs and who have already initiated protease inhibitor therapy, adding a NNRTI may be an important part of the puzzle in sustaining viral load suppression or lowering it to undetectable levels.

At the FDA accelerated approval hearing for nevirapine, the manufacturer said that there is cross-resistance with delavirdine. There may be cross-resistance between all of the NNRTIs. This is an important element in considering which treatment options to use now or save. For example, the creation of resistance from the use of nevirapine could cause cross-resistance with DMP-266.

Very soon, Pharmacia & Upjohn will be making available preliminary results of their

interaction studies of delavirdine with each of the 3 approved protease inhibitors. The information is not complete and needs to be interpreted for purposes of actual application. These initial interaction studies were done by Upjohn without the participation of Merck, Abbott or Roche. Merck will conduct their own interaction study to confirm the Upjohn data, and presumably Abbott and Roche will do the same. It is advisable to wait for the results of further research before adding a NNRTI to protease inhibitor therapy.

Taking inappropriate dosing combinations of delavirdine with a protease inhibitor can cause under- or overdosing. Use of a NNRTI with a protease inhibitor will alter the blood concentrations of each of the two drugs, because these drugs are all processed through the same CYT P450 system in the liver. Underdosing, which can occur from sub-optimal blood concentrations, can cause the development of resistance to the protease inhibitor or the NNRTI. Overdosing, which can occur from higher than desired blood concentrations, may cause toxicities. A potential toxicity from too high a blood concentration of nevirapine can be severe rash. Increasing the blood concentration of ritonavir or indinavir beyond recommended levels can cause difficult to manage side effects or toxicities.