ANTIRETROVIRAL-NAIVE SUBJECTS CHRONICALLY INFECTED WITH HIV-1: Triple therapy with nelfinavir in combination with AZT and 3TC -- Vancouver Abstract L.B.B. 6031, Martin Markowitz et al

"This study is testing the hypothesis: triple therapy with two nucleoside RT inhibitors and a potent protease inhibitor may erect an antiviral barrier such that durable suppression of measurable viral replication occurs. This in turn, should result in long-term immunologic benefit".

The study objectives are to explore:

- safety, efficacy and pharmacokinetics,
- to determine the significance of prolonged viremia,
- to understand the nature of CD4 and CD8 repopulation post-therapy,
- to model the 2nd phase of decay of free virus and virus producing cells.

Twelve antiretrovirus-naive HIV-infected subjects, with screening HIV RNA plasma viral load above 10,000 copies/ml, were started on therapy of:

- AZT 200 mg tid (every 8 hrs or 3X/day)
- 3TC 150 mg bid (every 12 hours or 2X/day)
- nelfinavir 750 mg tid (Agouron's protease inhibitor)

Baseline evaluations for the study group were:

- HIV plasma RNA:

  mean - 209,011 copies/ml (5.32 log)

  median - 81,270 copies/ml (4.91 log)

  range - 177,990 - 864,900 copies/ml (4.26 - 5.94 log)

- CD4 cell counts:

  mean - 258 cells/mm^3

  median - 253 cells/mm^3

  range - 37 - 557 cells/mm^3

Previous opportunistic infection: 1 had PCP out of 12 subjects.

HIV related conditions:

- 1/12 nephropathy and myopathy
- 1/12 eosinophilic pustular folliculitis
- 2/12 oral candidiasis
- 1/12 hairy leukoplakia

Safety:

- 1/12 withdrew at week 6 grade 4 elevation of CPK and for grade 2 diarrhea and abdominal cramping
- investigators said "triple therapy has been well tolerated with mild to moderate diarrhea, mild to moderate nausea and fatigue being the most common drug related adverse events"
- no other serious side effects

Virology

Changes in plasma RNA:
By week 8 the mean reduction in viral RNA in plasma was 2.6 log; by week 12, 11/11 were below the detection level of the RNA test being used (under 500 RNA copies/ml).

- the number of subjects below detectability:

  week 2 -- 2

  week 3 -- 2

  week 4 -- 7

  week 6 -- 8

  week 8 -- 10

  week 12 -- 11

  week 16 -- 11

RNA less than 25 copies:
The levels of plasma RNA were measured by a sensitive test down to a detectable level of 25 copies/ml. By week 8, the average RNA levels were below the detectability level of this test.

"Negativity in PBMC co-cultures (under 0.1 $TCID_{50}/10^6$ PBMC) have been achieved in all remaining 11 subjects by week 12 of therapy..... Following the predicted 2.0 log reduction in plasma RNA in the first 2-3 weeks, the second phase of viral decay was slower with a mean $T_{1/2}$ of approximately 17 days. Associated with this degree of suppression of viral replication, a mean and median increase of 109 and 98 (CD4)

cells/mm^3 is observed at 12 weeks."

Commentary:
It is important to note that, depending on an individual's viral load level prior to treatment, it can take up to 12 weeks before their viral load becomes undetectable by a commercially available test. The higher the pre-treatment viral load the longer it may take to become undetectable.

David Ho discussed in Vancouver the data he has gathered on the kinetics of the virus and CD4 lymphocyte turnover in vivo. From experiments conducted by Ho and George Shaw, of the University of Alabama- Birmingham, the widely discussed new theories of HIV pathogenesis or kinetics have emerged. Prior thinking was that there was a prolonged period of relative virus latency; this has been replaced with the thinking that ongoing, high-level viral replication takes place from the time of initial infection. This research says, as many as 10 billion new HIV virions are produced per day, with a half-life in plasma of 6 hours. CD4 cells, a principle target for the virus responsible for viral replication, are turning over in high number, and once productively infected, have a half-life of 1.6 days. The life-cycle of the virus, from infection of one cell to the production of new progeny, which infects the next cell, is 2.6 days.

Based upon this work, immediately following potent therapy (as in this case with AZT/3TC/nelfinavir), the "first phase" of viral decay, occurs where 99% of the free virus in plasma decreases exponentially in the first 2-3 weeks with a short half-life, consistent with the rapid turnover of virions and productively infected cells. A slower "second phase" of viral decay can take longer, and includes latently infected CD4 lymphocytes, and long lived cells, presumably which contribute less than 1% of virus in the plasma, but are clearly able to re-initiate the rapid cycles of viral replication detailed above. (***End of commentary***)

Data at week 16, for 11 study subjects:

Subject	baseline plasma RNA copies/ml*	HIV RNA copies/ml**	CD4	base CD4	current current PBMC co-cultures ($TCID_{50}/10_6$)
31	84,960	under 25 319	499	under 0.1	
32	864,900	"	75	130	"
33	242,900	"	557	502	"
34	21,800	"	430	463	"
35	18,230	"	226	312	"
37	37,150	"	190	251	"
38	17,990	"	312	491	"
39	81,270	"	194	357	"
40	551,000	"	37	131	"
41	34,240	"	280	495	"
42	345,600	"	117	152	"

[*] For this baseline RNA value, the bDNA 2nd generation test was used; its lowest level of measure is down to 500 copies/ml.

[**] For this measurement the bDNA 3rd generation test was used; it can measure to a level of detectability down to 25 copies/ml.

Resolution of HIV related condition

- resolution of HIV related myopathy
- marked improvement in HIV related nephropathy
- resolution of molluscum contagiosum
- marked improvement of eosinophilic pustular folliculitis
- resolution of oral hairy leukoplakia
- resolution of oral candidiasis
- no new HIV related infections or neoplasms over 25 weeks.

Ongoing experiments:

- *significance of prolonged viremia*:

  Lymph node:

  particles (RNA)

  viral activity (ms mRNA)

  infectivity (culture)

Individuals whose HIV RNA remain "undetectable" after 12 months will be asked to undergo a lymph node biopsy.

Immunological response to therapy:

- memory vs. naive - CD45 RO vs. CD45 RA, 62L
- cells in cycle - Ki67 positive CD4 & CD8
- HIV pathogenesis - mathematical modeling of 2nd phase of viral decay

"We conclude that triple therapy with AZT/3TC and nelfinavir mesylate results in uniform aviremia after three months of uninterrupted therapy and holds promise in pharmacologically controlling HIV replication in a human host."

Commentary. As you may know there has been some ontroversy surrounding the

possibility of long term suppression of HIV below detectability, and the possibility for "eradication" of HIV in the infected individual. Some observers at the Conference in Vancouver objected to the presentations and discussions related to this subject, saying they encouraged listeners to put too much stock into the potential for being able to achieve long-term suppression or eradication. Others felt the concepts are important to be openly discussed at a medical conference. A concern for everyone was whether or not the press would report about the discussion of this subject at the conference in a responsible way.

Although it is exciting that we are able, for the first time, to ask these questions, it is crucial to remember that it is premature to take these notions seriously; additional studies must be conducted to seriously begin to address these issues.