

NEWLY INFECTED SUBJECTS: Triple Therapy with AZT/3TC and Ritonavir

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This study was designed in December of 1994, when it became clear there is high viral replication at all stages of HIV infection.

Newly infected HIV-1 infected patients represent the ideal study population to determine whether HIV-1 infection can be eradicated with combination antiviral therapy. This is due to the homogenous nature of the viral population early in infection, the lower likelihood of multiply drug-resistant virus within the viral population, and, finally, the relatively intact status of the host immune function. To learn whether HIV-1 infection can be eradicated from a human host, 12 subjects newly infected with HIV-1 were recruited between August 1995 and February 1996".

Commentary-

An important question not adequately addressed by a study in newly infected individuals (nor the AZT/3TC/nelfinavir study of treatment-naive individuals) is the treatment and disease management of individuals with moderate or advanced disease with treatment experience, or for those who may have exhausted available treatment options except for protease inhibitors and non-nucleoside RT inhibitors. Although the indinavir trial of AZT/3TC/indinavir (study #035) in AZT-experienced, 3TC-naive individuals addresses treatment of a drug-experienced group, we need to design and implement trials that will more broadly explore optimizing treatment strategies for this group of individuals. I hope the research establishment will not become preoccupied with eradication" studies for newly infected or treatment-naive individuals, to the point of not paying adequate attention to those with more advanced disease.

In the past, individuals with advanced disease often-times appeared to be written off, by researchers, drug companies and even some activists. It is clear that with the advent of many new therapies including protease inhibitors, it becomes increasingly more likely that we can devise viable treatment strategies for individuals with more advanced disease.

However, the apparent early success of treating newly infected and treatment-naive individuals lends a measure of credibility to the notion of treating early and hard" for all others who may be treatment-experienced or more advanced; because, if its true that the success of treatment is a function of homogeneity of viral population, less resistant virus, and the status of one's immune function, then the earlier it is in the course of disease progression, for any individual, the more successful treatment may be, unless you are afraid of exhausting treatment options; but, many new drugs are currently in clinical

development: 1592U89, 141W94, nelfinavir, delavirdine, nevirapine (approved recently), DMP 266 (a non-nucleoside RT inhibitor), and others. In pre-clinical development are: the Upjohn protease inhibitor, ABT-378 (Abbott's new protease inhibitor) and others. Still, some are concerned about the utility of the subsequent use of a protease inhibitor after pre-treatment with a different protease inhibitor, if a measure of resistance develops to the first one used. (*end of commentary*)

Twelve newly infected study subjects were treated with--

- AZT 200 mg tid,
- 3TC 150 mg bid,
- ritonavir 600 mg bid.

Study subjects

All 12 had circulating plasma virus as determined by bDNA (2nd generation whose lowest level of measure is 500 copies/ml), and one of the following to indicate recent infection:

- a negative HIV-1 ELISA (1/12),
- an evolving Western Blot with progression of at least two bands (7/12), or
- a negative HIV-1 antibody test within 120 days of screening and a clinical history consistent with acute HIV-1 infection (4/12).

All subjects had symptoms of acute infection, three mild, six moderate, three severe. Nine of 12 identified a precise time of infection that preceded the onset of symptoms by an average of 15 days (range 6-20). Therapy was initiated on average 65 days after the onset of symptoms (range 40-126).

Baseline HIV RNA in plasma

- median baseline viral load: 10,423 RNA copies/ml (4.01 log)
- mean baseline viral load: 91,389 RNA copies/ml (4.96 log)
- range baseline viral load: 1,400 to 953,200 RNA copies/ml (3.15 - 5.98 log)

As you can see, some patients were captured at peak and some past peak", Dr. Markowitz said.

Baseline CD4--

- mean CD4: 633 CD4 cells/mm³
- range: 312 to 906

CD4/CD8 ratios were inverted at baseline with a mean of 0.75, with a range from 0.41 to 1.03.

Data for study subjects

patient	duration of therapy (months)	baseline CD4/C D8*	current CD4*	CD4/CD8*	Plasma RNA bsln./current [±]	Current PBMC co-culture (TCID50/106)
2	10	564/940	864	0.89	1420/under 500	under 0.1
3	6	312/303	344	1.48	3846/under 500	under 0.1
5	8	437/840	736	1.64	953,200/under 500	under 0.1
6	7	821/798	1205	1.33	39,190/under 500	under 0.1
7	6	423/1032	708	0.63	17,650/under 500	under 0.1
8	5	584/800	822	1.22	21,140/under 500	under 0.1
9	4	916/889	1095	0.95	2140/under 500	under 0.1
11	4	473/498	482	1.19	24,230/under 500	under 0.1
12	4	392/440	523	1.13	17,630/under 500	under 0.1

All study subjects have less than 100 equiv/ml as measured by a variety of research methodologies, including the Chiron 3rd generation assay (3.0). They all may also be below 25 RNA copies/ml.

* (cells/mm³), the baseline CD4/CD8 ratio for each of the subjects: pt #2--0.60, pt # 3--1.02, pt #5--0.52, pt #6--1.03, pt #7--0.41, pt #8--0.73, pt #9--1.03, pt #11--0.95, pt #12--0.89

** current ratio of CD4 to CD8

+ the plasma RNA measure in this column were results of bDNA 2nd generation, which measures to 500 equiv/ml.

Discontinuations: 3 study subjects withdrew from the trial: 2 due to non-compliance and 1 due an adverse event. First patient withdrew at 28 days due to adverse reactions to all 3 drugs. This person was taking the liquid formulation of ritonavir which was stopped at day 14 due to nausea and vomiting, and on day 28 he discontinued AZT/3TC due to myalgia and fatigue. One subject withdrew at 5 months due to inability to comply with taking study medications and the clinic visits, not due to adverse events; and, investigators dropped one person at 2 months for their inability to comply with study

visits. One subject was treated with AZT/3TC alone until month 7, when indinavir was added when it became commercially available; he developed a ritonavir allergy and investigators were not allowed to re-challenge him with ritonavir. There are 8 subjects who have been on triple therapy for 4-10 months, and also included, in the set of data, is the person who was on AZT/3TC with indinavir added.

Therapy is planned to continue for a minimum of 1 year, at which time lymphoid tissue will be sampled and then assessed for the presence of active viral replication.

After 12 months of continuous therapy, subjects with a minimum of 9 months undetectable" virus (by bDNA under 500 equiv/ml) and PBMC co-culture (under 0.1 TCID₅₀/10⁶ PBMC) will be asked to undergo lymph node biopsy to assess for persistent viral activity.

Decisions whether to continue therapy will be discussed and made by subject and principal investigator based on what is seen in blood, tissue, immune responses.

Dr. Markowitz emphasized that this is an ongoing experiment to test a hypothesis. It is premature to draw any conclusions yet. Many questions remain to be addressed.

Commentary

There are a number of compartments" where virus may be present, in addition to the lymph nodes. In Vancouver, other compartments about which we should possibly be concerned were identified and they include: testes, brain, CSF. David Ho discussed how difficult it is to adequately penetrate the brain. He said, even the therapies currently available to us that do penetrate the brain, are not adequately effective. Other researchers believe there are, in fact, sanctuaries" for the virus in these other compartments, and expressed doubt of the potential for emptying or eradicating" virus from these other compartments; while I believe Ho has stated there are no sanctuaries. As you can see, there are many remaining questions that need to be addressed.