



Maine AIDS Care

AIDS Consultation Service •

Maine Medical Center •

Spring 1995

New Optimism Regarding HIV Treatment

New insights into HIV viral dynamics, coupled with promising preliminary studies using new antiretroviral drugs and immune modulators has led to a renewal of cautious optimism for the management of HIV disease.

Two independent research studies suggest that HIV turnover is much higher than previously thought, and that the hosts' immunological reserve is also much greater than had been appreciated. These studies, undertaken in individuals with CD4 counts from ~30-500, demonstrated a very dynamic situation with the early production of billions of viral particles with a serum half-life of only 2 days. When viral production was temporarily halted, a significant rise in CD 4 cells was seen. The CD4 count doubled every 15 days when viral replication was interrupted by antiviral drugs. These studies suggest that immunologic reconstitution is possible if viral replication can be controlled. However, the very high viral turnover ensures a high mutation rate, leading to more rapid development of viral resistance to therapies.

It is hoped that trials of new antiviral drug combinations may provide more effective control of viral replication and delay development of resistance. In addition to combination therapy regimens using different reverse transcriptase inhibitors, there is a growing interest in protease

inhibitors. There are 4 or 5 new protease inhibitors that are in use or will soon be in Phase III trials. These drugs interfere with viral assembly within the host cell's cytoplasm. Their effect on viral load in several early trials was markedly greater than that seen with currently available reverse transcriptase inhibitors. In addition, four different trials demonstrate that the combination of AZT with lamivudine (3TC) shows promise as potentially synergistic agents in some patients.

While progress continues on the antiviral front, a report from the NIH on the benefits of interleukin-2 on CD4 counts (in patients with >200 CD4 cells) was published in the NEJM. Interleukin-2 therapy is costly and potentially toxic, but the results reported suggest a possible benefit of cytokine or anticytokine therapy in HIV disease. Phase III trials are currently underway to test the effectiveness of Interleukin-2, and to develop better tolerated cytokine regimens.

The newest thrust in antiviral therapy for HIV is the development of "antisense DNA" molecules that are designed to attach to conserved regions of viral RNA, blocking protein production and interfering with viral replication. One such "molecular bullet" is now in phase II trials, and others will soon be in phase I trials.

Managing the "Alphabet Soup" of Antiretroviral Therapy

Four anti-retroviral drugs, all reverse transcriptase inhibitors, are currently available for treatment of HIV disease. In general, treatment is usually offered to patients with CD4 counts of <500.

AZT or zidovudine is the drug of choice for initiation of therapy. If AZT is not well tolerated, treatment with DDI or DDC is usually recommended. The decision of whether to use DDC or DDI is usually based on their differing toxicities. DDI may cause pancreatitis, and therefore is usually avoided in patients with a history of pancreatitis or severe liver disease. DDC's primary toxicity is peripheral neuropathy.

If a patient tolerates AZT well, and if the CD4 count is stable, no change in therapy is necessary. However one study suggests a benefit with change to DDI therapy after 4 months of AZT even in the absence of clinical progression. If the CD4 cell count is falling steadily, DDI or DDC may replace AZT, or be combined with AZT.

Patients who have progressed on AZT, DDI, or DDC, may be switched to stavudine (D4T), the most recently approved reverse transcriptase inhibitor.

Another reverse transcriptase inhibitor, 3TC (lamivudine) looks promising in combination therapy with AZT. It is available through a

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New Measures of Viral Load Show Potential Role in HIV Therapy

New techniques to determine HIV viral load in the blood may facilitate the use of antiviral therapy. Monitoring the response of HIV infection to medical therapy has been difficult. Falling CD4 lymphocyte counts predict progression to AIDS and risk of opportunistic infections, but are an insensitive marker of antiviral response to therapy. Other surrogate markers such as P24 antigen (HIV Antigen) or Beta-2 microglobulin levels have some predictive value in determining progress, but have not proved to be very effective in month to month monitoring of patients on antiviral chemotherapy. Two new techniques for measuring HIV viral load are now available, and preliminary data suggests they may be useful in assessment of antiviral therapy. Both techniques utilize molecular systems for detection of HIV RNA. The branched DNA assay (Chiron) and quantitative polymerase chain reaction (PCR) appear to correlate well with each other. Results are reported as a number of viral particles per volume, and may range from undetectable to millions. Long term studies using these assays are underway, and there is currently little clinical outcome data available. However, it is likely that measures of viral load will become part of an emerging treatment strategy based on assessment of an individual's response to particular antiviral regimens.

Zidovudine (AZT) Prophylaxis After Percutaneous HIV Exposure - Update From CDC

Although there is no prospective data on the possible effectiveness of AZT prophylaxis after needlestick exposure, a recent abstract from the CDC (Abstract #586 2nd NIH Conference on Retroviruses, Washington DC) of risk factors for seroconversion among health care workers with percutaneous exposure to HIV suggests the possibility of benefit with AZT use. In this multivariate analysis of 700 health care workers with exposure, risk factors for seroconversion included visible blood on the needles, deep percutaneous exposure, a large diameter hollow needle, a source patient with AIDS or terminal AIDS, and a lack of AZT prophylaxis. Prior risk studies have not demonstrated any benefit from AZT prophylaxis, and the CDC has reported 8 cases of health care workers who have now converted despite AZT use. The CDC currently makes no recommendation regarding the use of AZT prophylaxis.

The usual protocol for AZT prophylaxis is the initiation of therapy as soon as possible following exposure (see insert) at a high dose (1200mg/d) for 6 weeks. A recent review from a NY Hospital reports on the acceptability of this regimen to health care workers (Farsiter et al. - Arch. Int. Med. 154: 2745-2749, 1994). Only 53% of health care workers chose to take AZT, and of those who did, only one-third completed the course of therapy. Treatment was discontinued (in most compassionate use program for patients with a CD4 count <100. cases because of side effects (nausea, headache, fatigue) of AZT. Significant hematologic toxicity was not observed.

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compassionate use protocol.

Current trials are comparing the effectiveness of initiation of therapy with drug combinations versus monotherapy. Theoretically, combination therapy offers benefits over monotherapy in the prevention of viral resistance and the preliminary data is encouraging, but the answer is not yet in. Based on preliminary data, some clinicians choose to start all patients on antiviral combination therapy.

It is hoped that newly developed tests of viral load (see accompanying article) will lead to more rational use of antiretroviral therapy by providing a method of rapidly assessing viral response to therapy. Until then, switching antiviral therapy depends primarily on detection of clinical changes in the patient that suggest failure of current therapy, or on the basis of a significant decline in CD4 counts.

Experimental Drug Availability in Maine

Delavirdine (U90)

Protocol 0017 - AZT & U90
(CD4 >200)

Protocol 0021 - DDI & U90
(CD4 <200)

Protocol 0023 - DDI, AZT & U90

AIDS Consultation Service,
Portland, ME

3TC

Compassionate Use
AIDS Consultation Service
& Stratogen Health
Portland, ME

IL-2

Owen Pickus, DO, Portland

Antiretroviral Therapy for HIV

Drug	Class of Agent	Dosage	Toxicity
Zidovudine (AZT)	Reverse Transcriptase Inhibitor	200 mg tid	Leukopenia, anemia, nausea, myopathy
Didanosine (DDI)	Reverse Transcriptase Inhibitor	2 100mg tabs bid (1 hour before meals or 2 hours after meals)	Pancreatitis, neuropathy
Dideoxycytidine (DDC)	Reverse Transcriptase Inhibitor	0.75mg tid	Neuropathy, esophageal ulcer
Stavudine (D4T)	Reverse Transcriptase Inhibitor	40mg po bid	Neuropathy (rare)
Lamivudine (3TC) (Experimental)	Reverse Transcriptase Inhibitor (? Synergy with AZT)	<i>To be determined by on-going studies.</i>	<i>To be determined by on-going studies.</i>
Delavirdine (Experimental)	Reverse Transcriptase Inhibitor (non-Nucleoside)	<i>To be determined by on-going studies.</i>	<i>To be determined by on-going studies.</i>

Cost of Antiretroviral Therapy

Drug	Dosage	Price* (Day)
Zidovudine (AZT)	200 mg tid	\$ 8.45
Didanosine (DDI)	200 mg bid	5.55
Dideoxycytidine (DDC)	0.75 mg tid	6.40
Stavudine (D4T)	40 mg bid	10.89 ¹

*Prices base on Maine Medical Center Pharmacy as of 06/19/95

¹CVS pharmacy 06/19/95

Measures of Viral Activity

Test	Use	Cost ¹
P24 Antigen (HIV Antigen)	1. Diagnostic-neonate, primary HIV syndrome 2. Surrogate marker viral activity.	\$ 94.00
Beta-2 Microglobulin	Markers of viral activity (to follow response to therapy).	\$ 49.50
CD4 Count	Measure of immune functions; prognostic indicator.	\$100.00
New Measures of Viral Load		
Branched DNA test to quantitate viral RNA	Monitor plasma viral load - response to treatment	\$200.00 (Chiron)
Quantitative PCR	Monitor plasma viral load - response to treatment	\$200.00 (Roche)

¹ Cost represent an approximate amount according to MMC Lab as of 06/19/95.

Protocol for Zidovudine Prophylaxis for Health Care Workers

1. Determine exposure risk.
2. Baseline HIV serology, repeated at months 1,3, & 6
3. Zidovudine to start as soon as possible (at least within 72 hrs):200mg po q 4 hrs x 6 weeks. Monitor CBC every week.

A Patient's Perspective: In An Experimental Drug Trial

by Mike Martin

Mike Martin is a 40 year old man from Southern Maine. He tested positive for HIV in 1988, most likely being exposed to the virus in 1985. He hasn't had any opportunistic infections associated with HIV and his T-cell count is about 500.

Mike writes and edits the client newsletter at the AIDS Project in Portland called "In The Affirmative". He is also editing a new client information booklet at The AIDS Project called "Now That You Know You're HIV Positive".

Mike is in a drug study at the AIDS Consultation Service (ACS) done with the UpJohn Company to test the effectiveness of a drug called U-90 (Delavirdine).

Signing up for a drug study that is expected to last two years is a real commitment. It took me a little time and a lot of thinking to make my decision back then. It is a little over a year since the study began and the time has passed very quickly.

The study is for a drug called U90 (Delavirdine) and in my wing of the study I take it in combination with AZT. I had not taken any antiretrovirals before starting in the study as my T-cell counts were pretty good and I had not had any infections associated with HIV. So starting the study meant starting two drugs, 18 pills a day.

Before starting the drug, I and my cohorts were interviewed, x-rayed, EKG'd, blood tested, and thoroughly briefed. Some of my cohorts take U90 in combination with DDI, while others of us are in the AZT wing. I admit that my biggest concern was the possible side effects of the drug. U90 has been known to cause a rash, while AZT can have a number of side effects such as headaches or nausea. To date, however, I have had no side effects whatsoever.

Of course, this is a double blinded study so neither I nor anyone at ACS knows whether or not I am actually getting the U90. There are actually four possibilities concerning the U90. I could be on a low dose, medium dose, high dose, or placebo. The only sure thing is that I am getting AZT.

The U90 must be taken alone without food for one hour before and one hour after taking. The AZT must be taken outside of these times, but can be taken with food. Also they should be taken spaced at eight hour intervals (or pretty

close to eight hours). Like all new medicines, the dose taking is tricky at times, timing the taking of each medicine and arranging to remember to keep up with the meds no matter where you are. It's tricky, but not impossible, and like most things, it is now a routine part of my life.

One year into the study, my T4-cell count and my percentage of T4-cells to total lymphocytes has stabilized at a comfortable spot. The T4 count and the T4 percentage are the two markers Dr. Smith and I watch, and have watched for years. My low T4 count was 446, my high 901; my T4% low was 24%, my high 40%. These have moved around over the years, and up until getting into the study, my T4% was slowly, but steadily, declining. My counts and percentages have stopped dropping and even risen a little bit. So far, the drug study has apparently been good for me.

Of course, I had no idea or guarantees what would happen when I joined the study. It was a shot in the dark at that point. And even today, I don't know if the good results I've gotten come from the U90, AZT, the combination of the two, or just a lovely placebo effect. My guess is that it's the drugs that are helping, but hey, I'm no doctor!

Anyway, the blood testing and exams continue. At first we were tested weekly, then every other week, then every four weeks, and now we are tested every eight weeks. The paperwork alone is enough to cause a hernia. Also, I can see how drug testing is so expensive, as the rules and regulations, the testing and exams, and the hours of work it takes to do the paperwork can add up to some serious money. Of course, I do not get paid for this, nor do my cohorts. However, we do get free lab work (much more extensive than just a T4 count), and free U90 (or placebo), and free AZT (and/or DDI). We got free pill boxes and tote bags, but frankly, expense was spared on those items.

Why did I decide to join the study? Why does anyone do this? First there is the humanitarian aspect. This is a potentially good treatment for people with HIV, but we'll never know for sure until it's been tested. This is a chance to do good for people in the future.

Second, there is the self-interest factor. This drug might help me (certainly it hasn't hurt) right now. Many of my

cohorts are in more need of treatment than I am and they joined the study with hopes for improvement now. My own thinking about my own situation was that with a pretty good T4 cell count and T4%, maybe this treatment would stop the slow, steady decline I was experiencing at a respectable level. I personally know of many people who have lived a long time with counts much lower than mine.

Third, and equally important, I already knew both Dr. Smith and Sandy Putnam. They administer the study, and I knew and trusted that they would not let any harm come to me. I knew that they would be monitoring my progress and would let me know exactly what was happening. Trust is very important.

So, in the end, I decided to join the U90 study for all of these reasons. It was a good humanitarian effort, might be good for me personally, and I felt no harm would come to me because I trusted the people doing the study. At best, it has helped. At worse, it would have not been helpful and I would have dropped out of the study had any adverse effects lingered.

The results of the study have been mixed, from what I have learned from my cohorts, but in my case it's been a plus, so I will continue until the study is over. Still, it wasn't the easiest decision I ever made, and I know that people agonize over this kind of decision. Still, those of us who have been in the study a whole year have a sense of accomplishment and maybe even a little pride in what we are doing for ourselves and for others. In the race against HIV/AIDS, it is a little step toward the big goal. These things take time, though time is pressing.

**For More Information
Regarding Experimental
Drug Trials in New
England.**

**Call the AIDS
Consultation Service
Provider Hotline at :**

(800)871-2701

World AIDS Cases	2,500,000*
National AIDS Cases	441,528 ¹
National AIDS Deaths	270,870 ¹
Maine AIDS Cases	612 ²
Maine AIDS Deaths	296 ²

* Estimated

¹ As of December 31, 1994

² As of March 31, 1995

HIV/AIDS Educational Sessions

07/17/95	"HIV in Women" Family Medicine Review Course Colby College <i>Sandy Putnam, RN,MSN,FNP</i>
08/01/95	Emergency Medicine: An HIV Update Colby College <i>Robert P. Smith, M.D.</i>
08/15/95	"HIV Disease" Thomaston Prison Rockland, Maine <i>Sandy T. Putnam, RN, MSN,FNP</i>
10/04/95	AIDS Update Emergency PA Conference Ramada Inn, Portland <i>Robert P. Smith, M.D.</i>

If you are providing an HIV/AIDS related educational session, please let us know at (207)871-2099.

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