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Maine AIDS Care (Winter 1995-1996)

Maine Medical Center's AIDS Consultation Service

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Maine AIDS Care

AIDS Consultation Service • Maine Medical Center • Winter 95-96

New Drugs, New Combinations Show Promise

Four new antiretroviral agents have been approved by the FDA since November 1995. Three of these drugs (saquinavir, indinavir, and zidovudine) represent a potent new class of antiretroviral agents, the protease inhibitors. The fourth, lamivudine (3TC) is a new reverse transcriptase inhibitor. In addition, newly released data from 3 different studies document the benefits of antiviral combination therapies over zidovudine (AZT) monotherapy. What impact do these events have on current therapy for HIV?

Benefit of Combination Therapy Supported

On the basis of 3 studies (ACTG 175, Delta I & II), it appears that AZT monotherapy is no longer the initial treatment of choice in asymptomatic patients. Combination therapy (AZT & DDI, AZT & DDC) or DDI alone, delayed the onset of AIDS and improved mortality in asymptomatic patients where AZT alone did not. What is not clear is what combinations will prove most effective. Of the currently available medication, AZT & DDI, AZT & DDC, and AZT & 3TC are all of proven efficacy. Others that show promise include DDI & D4T, and combinations that include protease inhibitors may prove to be the most effective.

Role of Lamivudine (3TC or Epivir)

Lamivudine, a reverse transcriptase inhibitor, has very limited effectiveness as monotherapy, but is synergistic with AZT, and appears to inhibit the development of AZT-resistance among strains. The combination of AZT and 3TC appears well tolerated and effective in early clinical trials. Lamivudine has few side effects, although nausea and neuropathy have been infrequently documented. A recent abstract suggests that lamivudine may be rarely associated with neutropenia or anemia in patients with low CD4 counts. However, as these patients had late stage HIV and were on an average of 4 medications, it is not certain that lamivudine induced these events.

The combination of AZT, 3TC, and a protease inhibitor (indinavir) were remarkably potent in a small trial of 26 patients, 24 of whom were rendered aviremic at 6 months.

Continued on Page 2 *New Drugs*

First Delavirdine (U-90) Study Results Presented

At a recent investigators' meeting in Washington, DC in January, the initial results of all 3 protocols for the UpJohn Delavirdine (DLV) study were presented. Data for 2,300 patients from all 105 sites (ACS at MMC is one of the national multi-center study sites) were presented on >400 patients who have ≥ 1 year in the study. As a number of Maine patients participated in this trial we provide a detailed summary of these results.

Summary of Results

1. **Protocol 0021 (AZT + DLV or AZT + Placebo in Patients with CD4 Counts >200 and AZT naive or < 6 Months Prior AZT Therapy):** Three different doses of delavirdine were randomized among the patients receiving the experimental drug (200mg tid; 300mg tid; & 400mg tid). Highest blood levels of delavirdine were seen in the patients receiving 400mg tid. The best sustained CD4 cell increase was seen in the patients receiving 300 & 400mg tid. The HIV RNA viral load was decreased by 1.0 log with the 400 dose at 4 weeks. There was an increase in viral load by week 8 to .5 log, but this .5 log overall decrease was sustained for 60 weeks. Therefore, UpJohn has made a decision to delete the 200mg arm; the 0021 protocol will be converting all patients to the 400mg tid dose. In addition, patients who are receiving only AZT + placebo or AZT and DLV 200mg or 300mg will be re-randomized to receive AZT+3TC+placebo or AZT+3TC+DLV 400mg tid. In addition, a Phase II (New Trial Design) will be implemented for approximately 450 patients in the following way:
AZT+3TC+(DLV placebo)
AZT+3TC+DLV 400mg tid
AZT+DLV 400mg tid+(3TC placebo)

see *Delavirdine* cont. on page 3

Save the Date

Wednesday, May 29, 1996

AIDS Consultation Service's 1996 HIV/AIDS Symposium

Speakers include:

Dr. Scott Hammer ~ NE Deaconess

Dr. Harvey Makadon ~ Beth Israel Hospital

Dr. Howard Heller ~ Mass General

AIDS Conference Offers Reason for Hope

The just completed Third Conference on Retroviruses and Opportunistic Infections in Washington, D.C. provided the stage for several new insights regarding the pathophysiology and management of HIV disease. A number of promising findings from the past 18 months were supported or confirmed by new research. Key components offering hope and excitement were:

1. Information on a new class of drug (protease inhibitors) as well as combinations of drugs that slow viral replication / regeneration significantly better than the standard monotherapies of the most recent past. (see *New Drugs* page 1)
2. Information on new tests that measure the actual amount of virus in the peripheral system as well as how the results of these findings can be used to manage treatment.

Antiviral Therapy

Data presented at the conference confirms that treating HIV infection with a combination of antiviral drugs is generally more successful at achieving more complete virus suppression, leading to longer disease-free intervals, increased CD4 cell counts, limiting the emergence of drug-resistant viruses, and treating established drug resistance. Combination therapy with selected reverse transcriptase inhibitors can lead to sustained antiviral efficacy and attenuated viral virulence.

Analysis of survival improvements with combination anti-viral therapy were analyzed from a number of clinical trial and observational studies (ACTG 175, Delta, Glaxo Wellcome Trial, the MACS, and the Amsterdam HIV). Although these studies had different designs and were conducted on different study populations, a broad theme was consistent across studies: 1- Among ARV-naive patients, initiation of combination antiviral therapy in intermediate stage disease can provide clinical and survival benefits that are superior to ZDV alone; and 2- among ARV-experienced patients, delaying changing therapy until late or very late-stage disease seriously reduces clinical efficacy of combination treatment.

A number of antiretrovirals (nucleoside RT inhibitors, non-nucleoside RT inhibitors, protease inhibitors, and others) are currently being studied in combinations of 2, 3, or more drugs. Use of measures of viral load, such as branched DNA (bDNA) and RNA polymerase chain reaction (PCR) assays, combined with studies on drug resistance development, will allow researchers to rapidly identify the most promising drug combination regimens.

Data presented using protease inhibitors in combination with several other RT inhibitors offered the most exciting combination treatment information to date. Initial data suggests that this combination will more completely suppress the virus than any antivirals we used in the past. The prevailing theme at the conference was that protease inhibitors in triple combination treatment (with 2 RT inhibitors) may very well become the standard of care of HIV in the future, influencing not only timing of therapy, but other issues like survival time, etc. (See front page article and insert for more detailed information).

Viral Load Testing Supported

Research data presented in a number of studies indicated that measures of viral load in the bloodstream are better predictors of an infected persons' future health than any previous laboratory test or calculation used to make a prognosis. Changes in viral load precede changes in CD4 cell count by 1-2 years and accurately predict disease progression. CD4 cell count and viral load do not always correlate. For example: a patient can have a high CD4 count and a high viral load. This patient would have a poorer prognosis than a person who had a high CD4 count and a low viral load. HIV RNA measurements were correlated with clinical endpoints and overall trial results in a virology substudy in 391 of the 2467 patients enrolled in ACTG 175. A tenfold (1-log) increase in viral load resulted in a 3.83 fold (aggregate endpoint) increased risk of AIDS, death, or 50% decline in CD4 cell counts, a 5.77-fold increase in risk of AIDS or death, and a 6.0 - fold increase in risk of death.

It was noted that plasma HIV RNA measurements will be useful for patient management (with 2 gathered 2 wks to 1 month apart to establish a baseline). However, the proportion of treatment effect explained by change in viral load has not yet been defined. A general theme at various presentations in the conference was that viral load needs to be decreased as much as possible, with a goal being to get a patient to <10,000 copies/ml or even aviremic. Several investigators sounded a note of caution that viral burden in the blood may not reflect viral pathogenesis throughout the body. In particular, since lymph nodes have been identified as the principle site of viral replication for much of the disease course, investigators have continued to examine HIV in lymph nodes via biopsies, and compared viral loads with plasma HIV RNA levels. Results have varied, with several studies reporting no parallel lymph node responses or slower viral clearance from nodes. Further study is needed in this area.

New Drugs, cont.

Protease Inhibitors Spark Excitement

Protease inhibitors, a new class of antiretroviral drug that act to prevent the formation of infectious virions at a point in viral assembly appear to present a very promising advance in antiretroviral treatment. Saquinavir, the first protease inhibitor to be released, has been on the market for several months. Two additional protease inhibitors, **indinavir** (Merck) and **ritonavir** (Abbot) were approved by the FDA on March 1, 1996. These drugs appear to be additive or synergistic when combined with reverse transcriptase inhibitors, and based on their effect on HIV plasma RNA levels, appear to be more potent than reverse transcriptase inhibitors. Resistance to protease inhibitors does not overlap with known genotypic resistance to RT inhibitors, and their toxicities are not overlapping. In fact, toxicity to protease inhibitors has been minimal, limited to mild GI intolerance, circumoral paresthesias, nephrolithiasis, and dysgeusia, and mild elevation in transaminase and triglyceride levels.

So what should be our strategy now that these drugs are becoming available? Guidelines do not yet exist. Preliminary data suggests that ritonavir and indinavir are the most potent protease inhibitors. Ritonavir decreased mortality and onset of opportunist infections by 1/2 in a group of over 1,000 late stage patients. Indinavir, when combined with AZT+3TC, rendered 24 of 26 patients aviremic when plasma RNA was measured. It is reasonable to believe that very low plasma HIV RNA levels will be associated with delayed disease progression. Therefore, these preliminary results have sparked excitement among clinicians caring for persons with HIV.

Where does this information leave us at this point? For now, initiation of therapy is still usually begun in patients with CD4 counts of <500, with the exception that some clinicians now favor treating patients with higher CD4 counts if they have a high viral load documented on 2 or more occasions. Secondly, recent data suggests that when therapy is initiated, combination therapy (AZT+DDI or AZT+DDC) is probably preferable to monotherapy. Based on the results of ACTG 175, monotherapy with DDI would be an acceptable alternative. The use of 3TC with AZT appears to be another option that is well tolerated. Whether or not to add the new protease inhibitors early in therapy, or to reserve them for patients when other therapies fail to suppress viral load or to stabilize CD4 counts, is an open question. In general, toxicity of these agents appears to be low, but data on their interactions with other commonly used drugs in HIV is still sparse.

Principles of Protease Inhibitor Use

1. Start with highest appropriate dose and avoid dose adjustment if possible.
2. Use in combination with other agents.
3. Be aware of drug interactions (see other side of insert).

New Antiviral Agents & Combinations

Class	Drug	Usual Dosage	Side Effects	Effective Regimens
RT Inhibitors				
Nucleoside	AZT (Zidovudine)	200 mg tid	Bone marrow suppression Myopathy GI symptoms	AZT AZT + DDI AZT + DDC AZT + 3TC <i>All regimens with or without a protease inhibitor.</i>
	DDI (didanosine)	200 mg bid	Pancreatitis GI intolerance Neuropathy	DDI DDI + AZT DDI + D4T (Z?) <i>All regimens with or without a protease inhibitor.</i>
	DDC (deoxycytidine)	0.75 mg tid	Pancreatitis (rare) Neuropathy Oral / esophageal ulcers	DDC DDC + AZT <i>All regimens with or without a protease inhibitor.</i>
	D4T (Stavudine)	40 mg bid	Neuropathy	D4T D4T + DDI (?)
	3TC (Lamivudine)	150 mg bid	GI intolerance Neutropenia (rare)	3TC + AZT AZT + 3TC + Protease Inhibitor
Non-Nucleoside	Delavirdine <i>(available through compassionate use only)</i>	400 mg tid	Rash GI intolerance	Delavirdine + AZT Delavirdine + DDI Delavirdine + AZT + DDI or DDC
Protease Inhibitors				
	Saquinavir	600 mg bid <i>(with food)</i>	GI intolerance Drug interactions	Saquinavir + 1 or 2 RT inhibitors
	Ritonavir	600 mg tid <i>(with food)</i>	GI intolerance Drug interactions	Ritonavir + 1 or 2 RT inhibitors
	Indinavir	800 mg tid <i>(with food)</i>	GI intolerance Nephrolithiasis (2-5%) Drug interactions	AZT + 3TC + Indinavir Indinavir + 1 or 2 RT inhibitors

Potential Drug Interactions - Ritonavir
(Data on Indinavir Not Available)

	Avoid	Alternative Treatment
Analgesic	meperidine (Demoral) piroxicam (Feldene) propoxyphene (Darvon)	acetaminophen (Tylenol) aspirin oxycodone (Percodan)
Cardiovascular (Antiarrhythmic)	amiodarone (Cordarone) encainide (Enkaid) flecainide (Tambocor) propafenone (Rythmol) quinidine	
Antimycobacterial	rifabutin (Mycobutin)	clarithromycin (Biaxin) ethambutol (Myambutol)
Cardiovascular (calcium channel blocker)	bepidil (Vascor)	
Cold & Allergy (antihistamine)	astemizole (Hismanal) terfenadine (Seldane)	loratadine (Claritin)
Gastrointestinal	cisapride (Propulsid)	
Psychotropic (antidepressant)	bupropion (Wellbutrin)	fluoxetine (Prozac) desipramine (Norpramin)
Psychotropic (sedative/hypnotic)	alprazolam (Xanax) clorazepate (Tranxene) diazepam (Valium) estazolam (Prosam) fluroepam (Dalmane) midazolam (Versed) triazolam (Halcion) zolpidem (Ambien)	temazepam (Restoril) lorazepam (Ativan)

*If you have questions regarding the use or
side effects of Protease Inhibitors call the
AIDS Consultation Service
Treatment Information Line @
1-800-871-2701*

HIV Patient Assistance Programs

Encouragement over new drug therapies for persons with HIV is often met with frustration when faced with the financial cost. It can be overwhelming for people to figure out on their own how to access medication assistance programs, when and how to apply for Medicaid, and what they will be expected to pay for themselves. A person with HIV or AIDS could easily deplete a lifetime of savings just in paying for medications. People with HIV/AIDS benefit from having their own case manager or social worker to assist them in accessing whatever assistance they are entitled to.

Most private insurers offer prescription drug coverage that includes coverage for HIV/AIDS drugs. A person who has Medicaid coverage will qualify for medication assistance with any FDA approved drug. The Maine Dept of Human Services' Drug Reimbursement Program (207-287-5060) provides reimbursement for some medication for patients with HIV who meet financial requirements and have no other way to pay for prescriptions, or are pending Medicaid coverage or reimbursement by an insurance plan. Drugs covered under this program include: Pentamidine, AZT, DDI, DDC, D4T, Acyclovir, Fluconazol, and Bactrim.

Following is a list of the pharmaceutical companies who offer HIV patient assistance programs for some of the newer medications mentioned in this newsletter.

These pharmaceutical companies will supply patients with drug if they meet income guidelines and are not eligible for or have exhausted Medicare, Medicaid, Ryan White Funds, and all other third party coverage. Applications must be completed by a physician with DEA number.

Epivir (3TC), AZT, Acyclovir

Glaxo Wellcome Co., Patient Assistance Program
PO Box 52035
Phoenix, AZ 85072
1-800-513-3028

D4T (Stavudine), DDI

Bristol Meyers Squibb
Patient Assistance Program
1800 Robert Fulton Drive
Roston, VA 22091
1-800-272-4878

Norvir (Ritonavir)

Abbott Pharmaceutical Co.
Patient Assistance Program
1-800-688-9118

Invirase (Saquinavir), DDC,

Roche HIV Therapy Assistance Program
340 Kingsland Street
Nutley, NJ 07110
1-800-282-7780

Crixivan (Inidinavir)

Merck Pharmaceutical Co.
Patient Assistance Program
PO Box 4 (WP35-258)
West Point, PA 19468-0004
1-800-672-6372

Delavirdine cont.

The general consensus is that DLV used in combination with AZT provides an effective and sustained decrease in viral load (.5 log) and a smaller but sustained increase in CD4 cell count (20-30 cells). The AIDS Consultation Service has patients who have been enrolled in this study for almost 2 years now. We are pleased to see that the initial results demonstrate a benefit of delavirdine therapy.

2. **DDI + placebo vs. DDI + DLV 400mg tid:** Preliminary results of this arm showed that DLV in combination with DDI decreased viral load initially .8-.9 log (vs. DDI to .4 log alone), with a .5 log sustained decrease x60 weeks. There was a sustained CD4 cell count increase of 10-25 cells above baseline at 60 weeks. However, although these results give evidence that the combination of DLV+DDI does suppress viral replication, it appears that this is so because AZT seems to delay resistance to DLV and vice versa.

No changes are planned in the this protocol at this time.

3. **Protocol #23 Salvage Protocol: DLV 400mg tid + AZT 500 mg + DDI or DDC - Triple Combination Treatment:** The results of this arm of the study (with data available on 200 patients) showed that the great majority of these patients were AZT experienced for 1-3 years, and DDI experienced for 3-24 months. patients could roll over into this protocol only if they had a 50% decrease in CD4 cells, an AIDS defining illness, or upon trial completion. The results showed that DLV works in triple combination therapy, with the strongest combination being DLV+AZT+DDI. These Patients had a 10-40 cell increase in CD4 cell counts and a 0.3-0.8 log decrease in viral RNA for ≥ 24 weeks. It was also concluded that it is best to switch to 2 new drugs when going to triple combination therapy; the effect on CD4 and viral load is greater with 2 new drugs.

The DLV study provides the largest data base to date for HIV RNA PCR and bDNA viral load results. We look forward to further data analysis. Please note DLV is now available in Open Label by contacting UpJohn Pharmacia Co.

Community Counseling Center's New AIDS Family Therapy Initiate Helps Persons with HIV and Their Families

Community Counseling Center's AIDS Family Therapy Initiative is a new, comprehensive family treatment program for Cumberland County residents who have been affected by the HIV/AIDS virus. This program includes family members, friends, and caregivers. The Initiative is designed to help individuals and their families deal with the many implications of HIV disease.

Families affected by HIV frequently handle very difficult issues such as loss and impending loss, the unpredictability of the disease, and the sometimes extraordinary demands of providing physical and emotional care for persons with HIV. Through this program, individual and group therapy is provided in a safe, supportive environment in which each family member can communicate, express feelings, and develop helpful ways of dealing with stress.

Any family member or friend who is part of a person with HIV/AIDS caregiving support network can participate in the program (the persons with HIV/AIDS does not have to live in Cumberland County). For more information, contact the AIDS Family Therapy Initiative Coordinator at Community Counseling Center, (207) 874-1030. Community Counseling Center is a United Way agency.

**AIDS Consultation Service
Provider Treatment
Information Hotline
(800)871-2701**

**Monday - Friday
8:00 - 4:00**



World AIDS Cases **4,500,000***
U.S. AIDS Cases **501,310**
U.S. AIDS Deaths **311,381**
Reported through 10/31/95 by CDC

Maine AIDS Cases **712**
Maine AIDS Deaths **335**
As reported through December 31, 1995

Upcoming HIV/AIDS Educational Sessions

April 23, 1996 Primary Care Management of HIV & Living with HIV

Central Maine Medical Center, Lewiston Maine
9:00 am - 12:00 pm

Sandra Putnam, RN, MSN, FNP Nurse Coordinator, AIDS Consultation Service

May 29, 1996 AIDS Consultation Service - HIV/AIDS Symposium

Maine Medical Center, Portland Maine
8:00 am - 4:00 pm

Topics & Speakers Include:

New Concepts in HIV and New Approaches to Antiviral Treatment

Dr. Scott Hammer - New England Deaconess Hospital

Primary Care Management - Applying the Newest Science to Disease Management

Dr. Harvey Makadon - Beth Israel Hospital

Opportunistic Infection Management

Dr. Howard Heller - Mass General

Afternoon Breakout Clinical Tracks Include:

1. **Pain Control, Depression, & Dementia - Challenges to Management in HIV**
2. **HIV in Women**
3. **HIV Update for People Living with AIDS - Answering All Your Questions**
(Panel presentation / discussion)

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