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AIDS TREATMENT NEWS

Issue Number 272
June 6, 1997

Published twice monthly by
John S. James
P.O. Box 411256
San Francisco, CA 94141
415/255-0588
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## Contents



# Limited Immune Recovery After Treatment with Antiretrovirals, IL-2;

## Interview with Clifford Lane, M.D.

by John S. James

A person's "CD4 count" (the number of CD4+ T-cells per cubic millimeter of blood) is used as a rough indicator of immune system health. But the CD4 cells which are counted are not all the same. In a healthy individual, there are a billion or more different kinds of CD4+ T-lymphocytes — each programmed to recognize only one specific antigen (foreign substance, such as part of a protein produced by a bacterium or virus).

In HIV infection, when the CD4 count becomes low (especially under 200), some of this "repertoire" of cells is lost; it is probably not immediately restored when the CD4 count rises in response to antiretroviral treatment (or to treatment with antiretrovirals plus IL-2 (Proleukin®), which causes growth of the CD4 cells which are still there). Eventually there may be some natural recovery of the repertoire — or researchers might learn how to restore the repertoire by cell transplantation. Meanwhile, it may be possible for the immune system to function adequately even though some of its diversity is lost.

On May 31 *AIDS Treatment News* interviewed Clifford Lane, M.D., Clinical Director of the U.S. National Institute of Allergy and Infectious Disease. Dr. Lane is senior investigator of a research team which published a recent paper on immune recovery after treatment of HIV with antiretroviral therapy, or with antiretrovirals plus IL-2.[1] To introduce the interview, we wrote the following background section to explain some of the immunology involved.

### Background: Different Kinds of CD4+ T-Cells

*AIDS Treatment News* often uses the term "CD4 cells" as a less complicated way of saying "CD4+ T-lymphocytes" — which is technically more accurate, since there are CD4 cells which are not T-cells at all. This article is only concerned with T-cells, however.

T-lymphocytes are often named according to the molecules on their surface. CD4+ T-lymphocytes are those immune-system T-cells which have the CD4 molecule on their surface; CD8+ T-lymphocytes have the CD8 molecule. Both cells also have antigen-specific receptors on their surface. Each cell has approximately 10,000 or more copies of its antigen-specific receptor molecules on the cell surface.

The billion or more different kinds of these cells are due to a billion or more variations in the T-cell receptor. These variations occur when the cell is formed (usually near the beginning of life, in the womb or in early childhood). T-cells begin as undifferentiated stem cells — special cells which are able to mature into any kind of blood cell. Certain stem cells are programmed by the thymus gland to become T-cells; when this happens, certain genes of the cell combine randomly, forming the immense number of different possible combinations. Many of the resulting receptors would cause the cells to attack the body itself, leading to autoimmune disease; these unwanted cells are

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AIDS TREATMENT NEWS

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## Contents



# Protease Inhibitors' Metabolic Side Effects: Cholesterol, Triglycerides, Blood Sugar, and "Crix Belly." Interview with Lisa Capaldini, M.D.

by John S. James

[In the last few months we have heard increasing anecdotal reports of a condition which has been named "Crix belly." People may gain 40 pounds or more of fat remarkably quickly in the lower abdomen, and there may also be some muscle wasting in the arms and legs. The cause is unknown. This problem was not seen before the use of protease inhibitors; it is not known if it is associated primarily with indinavir (Crixivan®), for which it was named, or if it may be caused by other protease inhibitors as well. Nothing has been published so far.

[Last month we asked Lisa Capaldini, M.D., an AIDS physician in San Francisco, what she was seeing that our readers should know more about. She said that more attention was needed to certain lipid (fat) and other metabolic problems which appear to be related to protease inhibitor therapy.

[The interview below was conducted on August 8, 1997 and went to press four days later. Because this information is so new, the picture could change rapidly over the next few weeks or months. Those seeing this article at a future time should seek out the most current information then available.]

**ATN:** What have you seen of metabolism problems with the protease inhibitors?

**Dr. Capaldini:** So far we have identified three metabolic disorders associated with protease inhibitor therapy as a class. First we saw high triglycerides; triglycerides are one of the two kinds of lipids, or fats, we measure in the blood. Most peoples' triglyceride level runs between 100 and 200. High triglycerides clinically can cause pancreatitis, and have been found to be associated with (but not necessarily cause) hardening of the arteries.

The second condition is high cholesterol in patients whose previous cholesterol levels have either been normal, or as is common with advanced HIV, low. The pattern of high cholesterol is elevation of the "bad" or LDL cholesterol, compared to the so-called "good" or HDL cholesterol. This is the unfavorable pattern of LDL to HDL cholesterol associated with hardening of the arteries, which can lead to heart attacks, strokes, and peripheral vascular disease.

The third condition is high blood sugar. Usually the levels are not high enough to cause symptoms or, to our knowledge, to cause any of the complications associated with diabetes. They are typically 110 to 150 — which is not normal, but is not in the range usually associated with symptoms, which would be over 250.

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AIDS TREATMENT NEWS

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## Contents



# Health Insurance More Available: Federal Legislation Effective July 1

by John S. James

New Federal laws which became effective on July 1 will make it much easier for persons with preexisting medical conditions to change jobs without losing health insurance, and will also help some people who do not now have health insurance at all.

The new legislation, the Health Insurance Portability and Accountability Act, became law on August 21, 1996, but many of its provisions were not effective until July 1. Some — but not all — of the protections of this law were already available through state law in California and some other states. (State laws may continue to provide additional protections beyond those of the Federal law.)

Here we quote from the Conference Report, which was passed by both houses of Congress in early August 1996, which authoritatively explains the law. We added our own notes with explanations and additional information. There are many more details, and expert advice will be needed in some cases. But anyone with a serious illness should be aware of the major provisions of the law.

From the Conference Report:

**"The Legislation Limits Exclusions for Preexisting Conditions.** The bill prohibits employers offering health coverage and health insurers from limiting or denying coverage to individuals covered under a group health plan for more than 12 months for a medical condition that was diagnosed or treated during the previous 6 months. Once the 12-month limit expires, no new preexisting condition limit may ever be imposed on people maintaining their coverage, with no more than a 63 day gap, even if they change jobs or health plans.

**"Employers and insurers must credit coverage of less than 12 months toward any preexisting condition exclusion under a new health plan.** For example, an individual who has had coverage for six months when he or she changes jobs or health plans would face a maximum additional exclusion of 6 months, rather than the normal 12 months...

**"The Legislation Prohibits Discrimination Against Employees and Dependents Based on Health Status.** The bill prohibits employers offering health coverage to employees or dependents from excluding an employee or dependent from coverage, to drop an employee or dependent from coverage, or to charge an employee or dependent higher premiums based on that individual's health status, medical condition, claims experience, receipt of health care, medical history, genetic information, evidence of insurability (including domestic violence), or disability."

Note: Employers do not have to offer health insurance at all. But if they do, their health insurer cannot exclude individuals based on their health status. They

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## Contents



# Delavirdine (Rescriptor®) Approved

By John S. James

On April 4 the FDA approved delavirdine (brand name Rescriptor) "for the treatment of HIV-1 infection in combination with appropriate antiretroviral agents when therapy is warranted." This drug, developed by Pharmacia & Upjohn of Kalamazoo, Michigan, is the second non-nucleoside reverse transcriptase inhibitor approved (the first was nevirapine — Viramune® — approved June 24, 1996).

Delavirdine must be used in antiretroviral combinations, because when it was tried alone, the virus developed 50-fold to 500-fold reduced sensitivity within eight weeks, in 14 of the 15 patients in that trial. HIV which is resistant to delavirdine is likely to be cross resistant to nevirapine and other non-nucleoside RT inhibitors; however, cross resistance is unlikely with protease inhibitors, or with nucleoside analog reverse transcriptase inhibitors (AZT, ddI, etc.).

The main side effect of delavirdine is skin rash. Rash attributed to the drug has occurred in 18% of patients in phase II and III controlled trials, and has been severe enough to cause permanent discontinuation of delavirdine treatment in 4.3%.

Certain drugs must not be combined with delavirdine; others, including some protease inhibitors, probably require dose adjustments. For more information, see the package insert.

## Approval History

The FDA's Antiviral Drugs Advisory Committee, meeting in November 1996, came to a tie vote on whether delavirdine should be approved — four in favor of accelerated approval, and four against. The reason for the ambivalence is the weakness of the data from those clinical trials which have been completed so far. On the other hand, there are suggestions that this drug might be important for some individuals, especially in combinations not yet tested in formal research. The trials which have been run were designed long ago, and did not study the combinations which would be chosen today. Three trials are reported in the FDA-approved package insert:

(1) In a one-year comparison of delavirdine plus AZT vs. AZT alone, the combination was significantly better than AZT monotherapy in reducing viral load. (But this information is less relevant today than when the trial was designed, since the comparison — AZT monotherapy — is inadequate.)

## *From the TelePort of:* 1775 " T " Street, NW Washington, DC

**Date:** Monday, July 13, 1998 **Number of Pages:** 6

**To:** Sandra Thurman, White House, Office of the AIDS Policy Director
**Fax Number:** 456-2438

**Memo:** You may find the attached recent data on AIDS treatments cost effectiveness trends of interest. • Bill Arnold, ADAP Working Group

File Treatment
3rd Drawer

# Access Project - Cost data

Articles and references from the AIDS Treatment Data Network Treatment Library:

[12264] Mortality and Health Care Costs for 6,297 AIDS Patients in California Before and After Protease Inhibitors

Mi Chen1 J. Rains1 G. Hiehle1 R. Hun1 J. Colford2

1Dept of Health Services, Office of AIDS 830 S Street, Sacramento, CA, 95814; 2U.C. Berkeley School of Public Health, Berkeley, CA, USA

Background and Objectives: Clinical trials have demonstrated reductions in morbidity and mortality among AIDS patients receiving protease inhibitors (PIs). Clinical trials are conducted on relatively small numbers of patients; those who volunteer to enroll may differ from the broader population. This study examines mortality rates and health care costs before and after the introduction of PIs in a large cohort of AIDS patients. Methods: We defined a cohort of 6,297 patients alive on 07/01/94 and present in both Medi-Cal (California's medical public assistance program) records and the California AIDS Case Registry. For each month beginning in 07/94, we determined mortality rates and health care costs for these patients. Results: For selected months:

| Month/Year | 07/94 | 12/94 | 07/95 | 12/95 | 07/96 | 12/96 |
|---|---|---|---|---|---|---|
| Number of patients in cohort | 6,297 | 5,166 | 4,095 | 3,538 | 2,995 | 2,787 |
| Number of patients receiving PIs | 0 | 0 | 0 | 75 | 1,151 | 1,374 |
| Mortality rate (per 100 person-years) | 42.8 | 44.9 | 31.2 | 34.5 | 17.8 | 10.6 |
| Hospitalization days (per 100 person-days) | 2.9 | 2.6 | 2.3 | 1.8 | 1.5 | 1.0 |
| Costs/patient/month (US$): | | | | | | |
| Inpatient | $727 | $726 | $521 | $468 | $324 | $156 |
| Outpatient | $472 | $394 | $390 | $329 | $294 | $198 |
| Pharmacy | $543 | $557 | $600 | $580 | $800 | $779 |
| Other | $217 | $187 | $167 | $131 | $166 | $128 |
| Total | $1,959 | $1,864 | $1,678 | $1,508 | $1,584 | $1,261 |

Conclusions: Prior to the availability of PIs, mortality rates and health care costs were declining for California AIDS patients receiving public assistance. Coincident with the explosion in the use of PI's in 1996, the decline became more dramatic. Our current research employs individual level analysis to examine the extent to which PIs (and other new therapies) were responsible for these improvements.

Source:

12th International Conference on AIDS, June 28-July 3, 1998, Geneva, Switzerland.

# Access Project - Cost data

Articles and references from the AIDS Treatment Data Network Treatment Library:

[60578] Decreased healthcare utilization costs with increased use of protease inhibitors in HIV+ patients

J.D. Stansell1 John D. Stansell2 D. Daly3 E. Hamel3 D. Lapins3

1San Francisco General Hospital, San Francisco California 94110; 2UCSF AIDS Program at San Fran General, San Francisco CA; 3Clinical Partners, San Francisco CA, USA

Objectives: To assess the effect of increased use of protease inhibitors (PIs) on overall healthcare utilization costs in HIV+ patients. Design: Blinded retrospective third-party claims review and chart audit. Methods: Data were collected from paid-claims insurance forms on use of PIs in 1996 and 1997 in 2336 HIV+ patients in 5 US regions (2 Western regions, Northwest, Southwest and Southeast). Forms were from HMO, fee-for-service, and PPO claims. Patients were classified by PI history and time since initiation of PI: (1) <1 year, (2) ≥1 year, or (3) not on PI. Costs per patient per month (PPPM) were compared by year, for each region and the group as a whole, in terms of cost of oral medications, professional fees, home healthcare, and hospitalization. PI use was also correlated with incidence of opportunistic infections (OIs): pneumocystis carinii pneumonia (PCP), Mycobacterium avium complex (MAC), and cytomegalovirus (CMV). Results: Between 1996 and 1997, PI use increased from 37% to 53% of the total population. For each 10% rise in PI use, there was a $76 increase PPPM in cost of oral medications but a $218 decrease in other costs (overall decrease: $142 PPPM). Costs decreased in all regions as PI use increased and tended to be lower where PI use was higher. PCP incidence fell from 5% to 1.9% (64% decrease). If PCP did occur, the cost of treating it was 40% lower in a PI than in a non-PI patient; costs were lowest in those taking PIs for ≥1 yr. MAC incidence decreased from 0.53% to 0%. CMV incidence, after falling markedly from 1995 to 1996, rose slightly, from 0% to 0.46%. Conclusion: Increased PI use correlates with a large drop in total cost of treatment of HIV+ patients despite increased initial cost of oral medications. Increased PI use also correlates with a significant improvement in outcome as measured by a decreased incidence of OIs.

Source:

12th International Conference on AIDS, June 28-July 3, 1998, Geneva, Switzerland.

# Access Project - Cost data

Articles and references from the AIDS Treatment Data Network Treatment Library:

[24121] Measuring the net hospital costs and physician billings for the last three years of life for HIV patients using a linked administrative database

David G. Schneider R.A. Hanvelt T.T. Copley N.L. Meagmer

BC Centre for Excellence in HIV/AIDS at St. Paul's Hospital 613-1018 Burrard Street, Vancouver, British Columbia V6Z1Y6, Canada

Objectives: To measure net hospital costs and physician billings for the last three years of life. Design: Retrospective using linked administrative data Methods: Incidence costs for hospitalizations and physician services are based on the British Columbia linked administrative database covering the period April 1985 to March 1996. Gross cost estimates are based on data for individuals with an ICD-9 code for HIV ever recorded on a hospital separation (ICD-9 HIV codes {042-044, 798.5} have been coded since 1987). Episodic cost are based on those who were deceased as of December 1995 based on Vital Statistic Records. This data file contains hospital and physician resource utilization data for 1807 HIV-positive individuals. In 1997, BC Vital Statistics reports 1874 person died due to HIV during the period 1987 to 1995. The sample selected based on hospital diagnostic information includes 96.4% of the reported HIV deaths in British Columbia. The missing cases may be due to reporting delays, under-reporting of HIV diagnoses, or that these cases never involved a hospitalization related to HIV. The net incidence resource use and costs are estimated by using an anonymous 1% sample of all individuals in British Columbia totaling 50,565 individuals. This sample provides a baseline estimate of direct costs for the general population at each age. Results: On average 93.4% of all acute hospital days (42.2/45.2 days) occur in the last three years of life. For years 1, 2, & 3 before death cummulative acute hospital costs are $24,000, $28,000 & $30,000 respectively. Aggregate physician costs are $4,350, $6,700 & $8,500 respectively. Total net costs are $28,200, $34,400 & $37,400 respectively. In the 3 years before death medical billings have remained constant over time & acute hospital days have decreased 19% from 1990/91 to 1995/94. In the final 3 months of life physician costs are $1,560 and hospial costs are $14,760 for a total cost of $16,320. Dollar amounts are 1997 standardized CDN. Conclusions: The nearly complete population sample minimizes bias. This is significantly different from most other cost studies which have smaller sample sizes and have generally sampled from within a clinical environment. Importantly, this sample likely includes those who might have a very limited interaction with the medical system. An expected positive cost bias in this literature is consistent with out findings. This study also shows that, on average, the vast majority of acute hospitalizations occur in the final three years of life.

Source:

12th International Conference on AIDS, June 28-July 3, 1998, Geneva, Switzerland.

# Treatment Library

## Access Project - Medi-Cal Data

Articles and references from the AIDS Treatment Data Network Treatment Library:

Uptake, Costs and Effectiveness of HAART

Author: John Phair, M.D.

The effectiveness of highly active antiretroviral therapy (HAART) in large populations was the focus of a series of papers presented Wednesday afternoon.

EuroSIDA, a cohort study of HIV-infected patients in Western European countries, documented regional differences in the initiation of three or more antiretroviral drugs and use of protease inhibitors in patients with less than 500 CD4 lymphocytes over 16 years of age. Therapy in three sub-cohorts selected in 1994, 1996 and 1997 was analyzed. Overall, the proportion of patients receiving no therapy or monotherapy decreased with time, and in 1997 there had been a 60% increase in triple drug therapy. The Central European region was the first to use protease inhibitors, but currently there is no difference in the utilization of HAART in Southern (SE), Central (CE) or Northern Europe (NE) [1]. Dr. Mocroft reported for EuroSIDA on regional differences in survival. After adjusting for age mode of transmission and CD4 cell number, CE had half the deaths at 18 months in persons with less than 200 CD4+ cells/mm3; in those with less than 50 CD4+ cells/mm3, survival was twice as long -- 40 months versus 19 months in SE and 23 months in NE [2].

Dr. Chene reported on clinical progression and adverse effects in a cohort of patients receiving protease inhibitors seen at 13 centers in France. This cohort was recruited in the spring of 1996. The median CD4+ cell count was 22 cells/mm3 and plasma viral load was >100,000 copies/mL; 90% of the 451 patients survived for 12 months. In a multi-variate analysis, prior AIDS and CD4+ cell count of < 20 cells/mm3 were the only determinants of progression or predictors of adverse events due to therapy. Choice of protease inhibitor did not influence progression or occurrence of adverse events in this model. However, indinavir use was discontinued less frequently, ritonavir was associated with the most adverse events and saquinavir with the most biologic failures [3].

The database of California's Medi-Cal Program was used to assess effects of HAART in 9,217 individuals. Outcomes included mortality and healthcare costs pre and post use of protease inhibitors in patients with AIDS and those with HIV infection. Monthly mortality rates per 100 person years in persons with AIDS fell from 60 in 1994 to 10 in June of 1997; 50% of the cohort used HAART. The HIV-infected group used less HAART but mortality decreased in this group as well. Overall, hospitalization decreased significantly, lowering health care costs, but pharmacy costs increased. Overall there was a moderate reduction in Medi-Cal expenditures in these patients [4].

At Yale, the development of an HIV/AIDS team was associated with decreasing hospitalizations and lowering of expenditures before introduction of HAART. These trends were accelerated with the availability of effective therapy in spite of an increasing number of patients cared for and the opening of a long-term care facility. Overall, the cost to the health care system remained stable; increased expenditures due to pharmacy, use of the outpatient clinic, plasma HIV RNA assays and the long term care facility were balanced by the reduction in admission of patients to the hospital and reductions in length of stay [5].

The Veterans Administration in the United States cares for more than 17,000 HIV/AIDS patients. A registry developed in 1992 has documented a reduction in deaths, morbidity, bed utilization and hospitalization costs since the introduction of HAART in late 1995. Outpatient clinic utilization and expenditures for antiretroviral agents has increased [6].

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Source:

12th International Conference on AIDS, June 28-July 3, 1998, Geneva, Switzerland. HealthCare Communications Group - Uptake, Costs and Effectiveness of HAART - Author: John Phair, M.D