FOIA Number: 2018-0755-F

FOIA MARKER

This is not a textual record. This is used as an administrative marker by the William J. Clinton Presidential Library Staff.

Collection/Record Group: Clinton Presidential Records

Subgroup/Office of Origin: National AIDS Policy Office

Series/Staff Member: Patsy Fleming

Subseries: National AIDS Strategy

OA/ID Number: 10183

FolderID:

Folder Title:
[Miscellaneous Correspondence] [3]

Stack:	Row:	Section:	Shelf:	Position:
S	66	5	10	3

November 1996

Dear Colleague:

Protease inhibitors are a new type of drug to treat HIV infection. These drugs, when taken in combination with other HIV therapies, offer great promise for people with AIDS. However, in order for these drugs to be most effective, doctors and patients must know how to use them properly. Enclosed is a packet of materials to provide information about protease inhibitors and other anti-viral drugs for you and your fellow staffworkers, clients, patients, health care providers, friends, etc. The packet contains materials created by four leading HIV treatment education programs. Please use them, photocopy them, call and ask for more as you need them. There is an enclosed card that tells you how to order more of these packets. Without the proper information, we will not be able to realize the promise that these new drugs may provide to people with AIDS.

Because these drugs are new, we still do not know enough about how to use them most effectively. There are three different protease inhibitors and five different nucleoside analogs. We do not yet know when is the best time to start therapy, which combinations are best to use first, how long the effect of these drugs can last, and what are the long-term side effects. The answers to these questions will come through continued clinical research and experience. But that takes time. Meanwhile, people with HIV are faced with treatment decisions today. Many people have no time to wait and must consider whether or not they will start an anti-viral regimen now or in the near future. This packet provides the information that is currently available to assist doctors and patients in making and following through on these difficult decisions.

In sending out this packet, none of our organizations are endorsing any of these drugs or a particular regimen. The decision to use these drugs is one that only each patient, in consultation with his or her doctor can make. However, without the necessary information, patients cannot begin to decide for themselves what they think is best. That is why we are sending this packet out all over the country.

These materials are meant to reach people at different reading levels. Several of them are in both English and Spanish. We are working to translate many of these materials into other languages. Feel free to copy any and all of them. We will keep supplying them until we have no more. We will update the packets as new information becomes available.

This is the first time that our organizations have worked in collaboration to provide treatment education materials. The mailing house that is coordinating this mailing for us is handling the mailing lists from each of our organizations. The mailing lists remain strictly confidential. The mailing house will not allow anyone to have access to these lists and we are not sharing our lists with each other.

We feel that the information provided is very important and we are committed to doing everything we can to help people learn about HIV treatment as quickly as possible. If you have any suggestions or comments on this packet, please call any of our organizations at the numbers listed below. Thank you for your support.

Yours truly,

Moises Agosto - National Minority AIDS Council
David Barr - Gay Men's Health Crisis
Martin Delaney - Project Inform
Ken Fornataro - AIDS Treatment Data Network

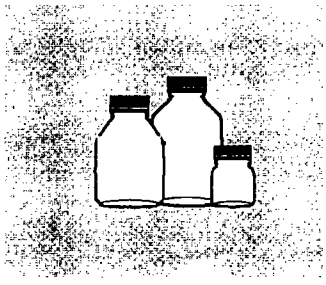
Clinton Presidential Records
Digital Records Marker

This is not a presidential record. This is used as an administrative marker by the William J. Clinton Presidential Library Staff.

This marker identifies the place of a publication.

Publications have not been scanned in their entirety for the purpose of digitization. To see the full publication please search online or visit the Clinton Presidential Library's Research Room.

COMBINATION THERAPY



THE SIMPLE FACTS PROJECT

Combinations of protease inhibitors are now being studied for the treatment of HIV infection. A study of ritonavir and saquinavir is ongoing, and a study of saquinavir and indinavir is planned. Data from just six weeks of the saquinavir and ritonavir study has been presented. Doses studied so far have been 400 mg of saquinavir twice daily with ritonavir at either 400 mg twice daily, or the standard ritonavir dose of 600 mg twice daily. The combination seems safe so far, but researchers recommend waiting for further results before trying combinations of protease inhibitors.

•

The Simple Facts Project is a program of the AIDS Treatment Data Network (The Network). This information does not intend to promote or endorse any specific treatment for any health related condition.

The most commonly prescribed anti-HIV treatment has been the drug AZT (brand name Retrovir). Other anti-HIV drugs that work in a similar way to AZT are ddI (Videx), ddC (Hivid), d4T (Zerit), and 3TC (Epivir). These drugs are known as nucleoside analogs. A newer class of anti-HIV drugs are protease inhibitors. The approved protease inhibitors are saquinavir (Invirase), ritonavir (Norvir) and indinavir (Crixivan). Recently completed studies clearly show that combinations of these anti-HIV drugs are much more effective than AZT alone in preventing disease progression and death.

The first studies to show the benefits of combination therapy were called DELTA and ACTG 175. These studies compared combinations of AZT with ddI and AZT with ddC to AZT taken alone. Several thousand people took part in these studies. People taking the combinations survived longer and had less disease progression than those taking AZT alone.

Since these studies were done, protease inhibitors have become available. A new test for measuring how well anti-HIV drugs are working is also available. The test is called the viral load test, and measures the amount of HIV in the blood. Researchers are finding that the level of HIV in the blood is linked to a person's risk of getting sick. A study has shown that using drug treatments to lower the level of HIV can reduce the chances that a person will get sick.

These new discoveries are changing the way doctors think about HIV treatment. Combination anti-HIV treatment is now the standard of care for people with HIV. We still don't have enough experience to know which anti-HIV drug combination works best, or for the longest time. What is known is that the stronger the anti-HIV effects of a combination therapy, the less likely it is that HIV will become resistant to the effects of the drugs. When HIV becomes resistant to a drug, that drug no longer works against the virus. This has led many doctors to use three drug combinations. Combinations usually include a protease inhibitor, 3TC, and one other nucleoside analog anti-HIV drug such as AZT or d4T.

The decision about which combination of anti-HIV drugs may work best for an individual is usually based on several factors:

- Which combination has the best chance of reducing the amount of HIV in my body for the longest time?
- Which combination will best increase my T4 cell count or keep it stable and hopefully prevent disease progression?
- What are my options if this combination stops working?
- What are the possible side effects of the drug combination?
- How many pills will I need to take?
- What symptoms do I have now?

Each of these questions may be part of the decision making process.

The best time to start combination therapy is not yet known. The new viral load tests may be helpful, as studies have shown the risk of disease progression is higher when the viral load is above 10,000. Most trials of anti-HIV drugs have also found benefits to treatment when the T4 cell count has dropped below 500. Because medication to prevent an opportunistic infection called PCP is needed when the T4 cell count goes below 200, anti-HIV treatment is usually considered before the T4 cell count gets this low.

Studies of different combination therapies are ongoing. Call the Network if you need a referral. The Network also has up-to-date fact sheets on the individual anti-HIV drugs and the newly approved viral load tests. Call us to receive free copies.

September 1996

Clinton Presidential Records
Digital Records Marker

This is not a presidential record. This is used as an administrative marker by the William J. Clinton Presidential Library Staff.

This marker identifies the place of a publication.

Publications have not been scanned in their entirety for the purpose of digitization. To see the full publication please search online or visit the Clinton Presidential Library's Research Room.

GMHC GAY MEN'S HEALTH CRISIS
treatment ISSUES
NEWSLETTER OF EXPERIMENTAL AIDS THERAPIES
VOLUME 10, NUMBER 2 FEBRUARY 1996

Protease Inhibitors Come of Age

by Theo Smart

The big news at the Third Conference on Retroviruses was the extraordinary antiviral and clinical effects achieved by protease inhibitors when administered along with nucleoside analogs. The reports, although limited in their scope, suggested that combinations of anti-HIV drugs now available will be considerably more effective than the mediocre HIV treatment options of the past.

In one study, Abbott's ritonavir (brand name Norvir) was found to dramatically prolong survival and slow disease progression in people with advanced AIDS. Other trials found that Merck's indinavir combined with several nucleoside analogs can hold HIV blood levels for many months below minimum detectable levels (less than 500 copies of HIV genes (RNA) per ml of plasma).

Findings from the Ritonavir Clinical Study

Abbott, which was running behind Merck and Hoffmann-La Roche in the race to develop protease inhibitors, is so far the first and only company to show that its drug extends survival and delays opportunistic infections (abstract LB6a). The company accomplished this feat by counting the clinical events that occurred in 1090 volunteers with advanced HIV disease—CD4 cell counts of 100 or below—randomized to take either ritonavir (600 mg) or placebo twice daily. The participants had a history of more than nine months of prior anti-HIV therapy and added ritonavir to their existing regimen of nucleoside analogs (most commonly AZT or d4T—3TC was not yet approved).

At baseline, the median CD4 cell count was 18 in the ritonavir arm and 22 in the placebo group. The median HIV plasma viral load was over 250,000 copies per milliliter. After completing four months on the study, trial participants who reached an AIDS-defining event were given open-label ritonavir.

When planning the study, Abbott researchers had calculated that it would take only 191 clinical events (the appearance of new opportunistic infections) or deaths to show definitively that ritonavir had an effect. That figure was reached within one month, although the trial continued while the company confirmed each event. When the results were analyzed, it became clear that the people on ritonavir were doing better than those on placebo within ten days. After one month, only 69 opportunistic infections or deaths had occurred in those receiving ritonavir as opposed to 149 in those on placebo, a statistically significant difference. Forty-four of these events were deaths—seventeen on ritonavir, and 27 on placebo.

After a median of six months follow-up (see table), 26 people on ritonavir versus 46 people on placebo had died, a 43 percent reduction in mortality. New OIs or death occurred in 85 people on ritonavir and 181 on placebo.

Viral load response was analyzed in 159 patients from the trial. Levels of virus decreased by 96 percent in the ritonavir arm but over time returned back upwards toward baseline. The trial's rapporteur, John Leonard, M.D., of Abbott, argued that virologic responses might have been more sustained if trial participants had begun their concurrent therapies at the same time as they started ritonavir. CD4 and CD8 cell responses (followed in 215 participants) were also significantly better in those taking ritonavir (47 CD4 cells and more than 200 CD8 cells above baseline at week sixteen).

An Australian team led by David Cooper, M.D., performed a more in depth exploration of the immunologic effects of ritonavir in 21 patients from an earlier trial by analyzing the functional responses of the new CD4 and CD8 cells (abstract 232). The team determined that the new CD4s acquired during the first four weeks of therapy were primarily clones of existing memory cells (lymphocytes that respond to previously encountered pathogens), and that new "naive" cells (which might be able to mount an immune response to infections for which there is no pre-existing defense) were noted only after the first four week period.

CD8 cells increased here too (abstract 451). Andrew Carr, M.D., one of the Australian team, noted that ritonavir's ability to increase CD8 cell counts has no parallels in the CD8 responses

Clinton Presidential Records
Digital Records Marker

This is not a presidential record. This is used as an administrative marker by the William J. Clinton Presidential Library Staff.

This marker identifies the place of a publication.

Publications have not been scanned in their entirety for the purpose of digitization. To see the full publication please search online or visit the Clinton Presidential Library's Research Room.

National Minority AIDS Council

Treatment ALERT

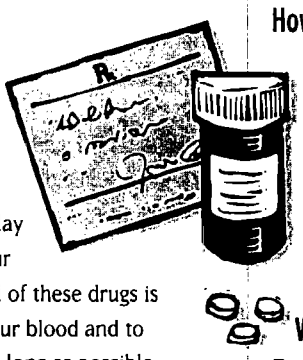
FALL 1996

HOW TO USE PROTEASE INHIBITORS THE RIGHT WAY

by Moisés Agosto

This issue of NMAC's Treatment Alert focuses exclusively on protease inhibitors and the best way to use them, to maximize their benefit. We encourage you to read this carefully and to distribute copies to people living with HIV who are taking or considering protease inhibitors.

Treating HIV infection



People living with HIV who are considering treatment must always be informed about their options. To treat HIV infection, doctors use drugs called antiretrovirals. These drugs delay the production of the virus inside your body in different ways. The main goal of these drugs is to decrease the amount of virus in your blood and to increase the number of T_4 cells for as long as possible.

What kind of treatments are available?

There are three kinds of drugs used to treat HIV infection. The first kind are the nucleoside analogues: AZT or Retrovir™, ddI or Videx™, ddC or HIVID™, D_4T or Zerit™ and 3TC or Epivir™. The second kind are non-nucleoside analogues such as nevirapine or Viramune™. The third and the newest kind are the protease inhibitors. The names of the protease inhibitors that are approved are saquinavir or Invirase™, ritonavir or Norvir™ and indinavir or Crixivan™. Notice that each of these drugs has two names. One is the generic name and the other is the brand(™) name.

What are protease inhibitors?

Protease inhibitors are a new class of drugs that are used to treat HIV infection. People living with HIV have the option of using three protease inhibitors currently available with a prescription from your doctor. They are Invirase™ (saquinavir), Norvir™ (ritonavir) and Crixivan™ (indinavir). In order to benefit from the use of these new protease inhibitors, people living with HIV must look for information and be aware of a few things:

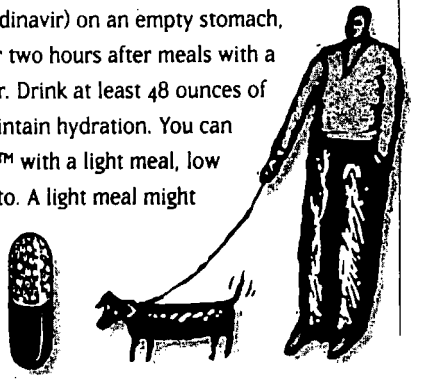
How can Protease Inhibitors improve my health?

Protease inhibitors slow the replication of HIV in your body. So far, the use of protease inhibitors in combination with other drugs like AZT, ddC, 3TC, D_4T or ddI may significantly reduce the amount of virus in your blood and give you a remarkable increase of T_4 cells. If your T_4 cells have a significant increase and the amount of virus is reduced considerably, your health may improve.

What is the best way to use Protease Inhibitors?

To make sure your body gets the full benefit from protease inhibitors, you must be aware of the things you can do to help your body to better absorb these drugs.

- Take Invirase™ (saquinavir) within two hours of a full meal or substantial snack.
- Take Norvir™ (ritonavir) with a full meal that is high in fat and protein.
- Take Crixivan™ (indinavir) on an empty stomach, one hour before or two hours after meals with a large glass of water. Drink at least 48 ounces of liquids daily to maintain hydration. You can take your Crixivan™ with a light meal, low in fat, if you need to. A light meal might be plain toast with juice or skim milk.



Clinton Presidential Records
Digital Records Marker

This is not a presidential record. This is used as an administrative marker by the William J. Clinton Presidential Library Staff.

This marker identifies the place of a publication.

Publications have not been scanned in their entirety for the purpose of digitization. To see the full publication please search online or visit the Clinton Presidential Library's Research Room.

PROJECT inform

Project Inform Fact Sheet

Protease Inhibitors

9/96

Update on Protease Inhibitors

New data on combination therapies and protease inhibitors show the most potent antiviral effects yet seen. Combination therapies which include protease inhibitors appear to suppress HIV replication and increase CD4+ cell counts to a greater degree and for a longer time that any previous therapies. Three protease inhibitors have been approved by the FDA - indinavir (Crixivan® from Merck), ritonavir (Norvir® from Abbott), and saquinavir (Invirase® from Hoffman La-Roche) - and several more are in development. All have been tested in a variety of ways and are widely available. They are not, however, interchangeable and there is nothing magic in the fact that a drug is a protease inhibitor. In the end, what matters is how well it works, not what label it wears.

Each of the drugs offers a different level of benefits and side effects. Each must be used wisely and with greater care than the previous generation of drugs if people are to get the maximum benefit offered by these therapies. Knowledge of how best to use them is limited but it grows with each month as additional studies report new data. The purpose of this article is to summarize the most important data from clinical trials. A second Project Inform document, entitled *"Developing Long Term Treatment Strategies"* discuss how to incorporate these drugs and other drugs into a treatment strategy.

What is a protease inhibitor?

A protease inhibitor is an antiviral drug designed to reduce the amount of HIV being produced in the body.

How are they different from other antiviral drugs, like AZT, ddI, d4T, 3TC and ddC?

Protease inhibitors attempt to stop HIV-infected cells from making effective new copies of the virus. The other drugs attempt to stop the virus from taking over a cell in the first place. By using such drugs together, the virus is blocked in two separate ways.

Why are they used in combination with the older drugs?

Combination therapy increases the overall effectiveness of the drugs and suppresses the development of drug resistance.

Are all protease inhibitors alike? Does it matter which one I use?

The three available protease inhibitors differ widely in their effectiveness, toxicity, and ease of use. They are similar in name only. Your choice of a protease inhibitor matters a great deal.

Indinavir Studies

Results from new studies of indinavir show that it combines particularly potent antiviral activity with a quite modest side effect profile. The studies evaluated the drug in people with little or no history of antiretroviral therapy use as well as in people who had been on AZT for six months or longer.

Study 1

Seventy-eight people with CD4+ counts between 50 and 200, viral load greater than 20,000 copies of HIV RNA and less than two week prior use of AZT or ddI received either AZT + ddI, indinavir alone, or indinavir + AZT + ddI. Results are seen in **Table 1.** The data suggest that people using all three drugs will fare better than those using indinavir alone or AZT + ddI.

Study 2

Ninety-seven volunteers with CD4+ counts between 50 to 400, viral load above 20,000 and at least six months prior use of AZT received either AZT + 3TC, indinavir , or a combination of all three. Results are shown in **Table 2.**

It is clear that those receiving the triple

Table 1 - Indinavir (IND), AZT, ddI

Therapy group	Maximum VL drop	Median VL drop @ 24 wks	Med. CD4+ increase @ 24 wks	% with at least 2 log VL drop	% with virus below LD
AZT + ddI	1.6 logs*	0.5 logs	30	20%	15%
IND	2.0 logs	0.5 logs	100	20%	15%
IND + AZT+ddI	2.9 logs	2.9 logs	100	80%	60%

Table 2 - Indinavir (IND), AZT, 3TC

Therapy group	Median VL drop @ week 24	Median VL drop @ week 48	Med. CD4+ gain @ week 24	Med. CD4+ gain @ week 48	% with virus below LD @ week 24	% with virus below LD @ week 48
AZT + 3TC	-0.6 logs	-0.4 logs	14	14	0% (0 of 27)	0% (0 of 8)
IND	-1.3 logs	-1.6 logs	106	158	41% (11 of 27)	56% (5 of 9)
IND+AZT +3TC	- 2 logs	-2.3 logs	127	218	90% (27 of 30)	89% (6 of 7)

VL = viral load LD = Limit of Detection

1965 Market St., Suite 220
San Francisco, CA 94103

Administrative Offices
415-558-8669

Fax
415-558-0684

Local Hotline
415-558-9051

National Hotline
800-822-7422

Clinton Presidential Records
Digital Records Marker

This is not a presidential record. This is used as an administrative marker by the William J. Clinton Presidential Library Staff.

This marker identifies the place of a publication.

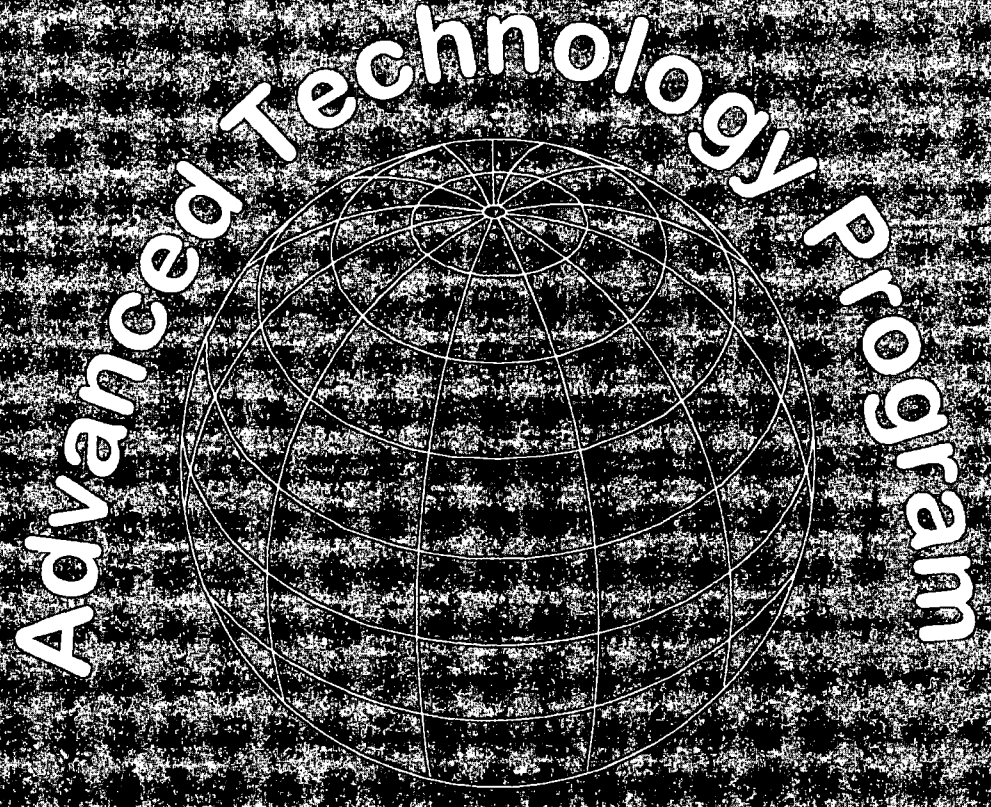
Publications have not been scanned in their entirety for the purpose of digitization. To see the full publication please search online or visit the Clinton Presidential Library's Research Room.

NIST

United States Department of Commerce
Technology Administration
National Institute of Standards and Technology

ATP Focused Program
Competition 97-07

TISSUE ENGINEERING



February 1997