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Statement of Purpose:
AIDS Treatment News reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations which work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

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Garlic Reduces Saquinavir Blood Levels 50%; May Affect Other Drugs

by John S. James

A study at the U.S. National Institute of Allergy and Infectious Diseases found that garlic supplements reduced blood levels of the protease inhibitor saquinavir by 51%. The garlic preparation, an amount equivalent to about two 4-gram cloves per day, was taken for 21 days by healthy HIV-negative volunteers. Then saquinavir was given for four days, and compared to a baseline four-day saquinavir dosing before the garlic was started.[1]

Later, after a 10-day washout with no saquinavir and no garlic, the volunteers were given a third 4-day dose of saquinavir. Even after 10 days off garlic, the saquinavir blood levels after a third four-day dosing only reached 60-70% of the original baseline blood levels -- indicating a persistent effect of the garlic.

Other findings of this study are complex, and the mechanism of this interaction is not clear. It probably involves the body's CYP450 enzyme system, yet the garlic appears to be affecting the oral bioavailability of saquinavir, not its elimination from the body. And there were two distinct groups of volunteers in how the garlic affected them. Most had a big decline in saquinavir levels after the 21 days of garlic use, with good recovery after the 10-day washout period. But three volunteers did not have a significant decline in saquinavir blood levels during the 21 days of garlic use -- but did have a big drop after the washout.

It is not clear how other drugs besides saquinavir will be affected. One study failed to find a statistically significant interaction with ritonavir, which affects the CYP450 enzyme system differently; however, that study used only four days of garlic treatment.

Saquinavir study co-author Judith Falloon, M.D., said, "We saw a definite, prolonged

interaction. The clear implication is that doctors and patients should be cautious about using garlic supplements during HIV therapy."

Comment: Do Companies Care If Their Drugs Work?

Clearly we need more drug interaction studies to guide physicians and patients in how to use medications -- especially when there is reason to suspect an interaction, or when a supplement is in wide use by those taking a certain medication. Drug interaction studies are usually small, inexpensive, and easy to do; this one, for example, had only 10 volunteers (six women and four men -- one woman was excluded from analysis due to lack of adherence), and each volunteer took the drug for a total of 12 days, reducing both side effects and expense.

We are fortunate that the U.S. National Institutes of Health tested garlic, a supplement widely used by people with HIV -- and found that it cut blood levels of saquinavir in half. This interaction could lead to drug failure and development of viral resistance, just as if patients cut their doses in half before taking them. Effects of garlic (and most other supplements) on other protease inhibitors are currently unknown.

While NIH should be commended, we need to ask why manufacturers don't do more interaction testing as a matter of course. Antiretrovirals are premium products with huge profit margins, costing thousands of dollars a year -- prices supposedly financing research and development. And more importantly, these are critical medicines that can determine whether patients live or die.

Yes, there are many supplements and even more approved drugs, but not very many are widely used by persons with HIV. And serious interactions are often fairly predictable from what is already known about the pharmacology of the drugs and supplements. Interaction testing is usually fast and cheap -- and none need be done on antiretrovirals that don't make it, only on those soon to be approved and marketed. What is needed is ongoing strategic initiative to identify potentially serious problems and spend a little money to head them off before they happen -- not years later.

Aside from the impact on human health, testing the most obvious potential interactions would contribute to the bottom line. Companies don't benefit when their drugs fail and patients stop using them, and their doctors and other doctors become less likely to choose those drugs for other patients. After paying all the costs of developing antiretrovirals and marketing them, when companies finally get a chance to make a profit, they are throwing much of it away.

The problem is that corporations do not act in their long-term interests unless they are organized to do so. Groups within companies are afraid of generating bad news. They may not realize that this bad news is really good news, because it allows them to make their drug more successful in the real world by targeting those patients most likely to benefit.

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NIH 7-Day On-Off Trial May Reduce Drug Side Effects, Cost; Why It's Not Ready for Use

by John S. James

On December 4 researchers at the U.S. National Institute of Allergy and Infectious Diseases published an early report of their 7-day-on/7-day-off trial of antiretrovirals.[1] This study found that a handful of selected patients, with a selected antiretroviral regimen, were able to use the drugs intermittently, with a schedule

of 7 days on and 7 days off. They were able to maintain viral suppression for 32-68 weeks so far, with only half the drug use and clearly reduced side effects. The researchers emphasize that this regimen is not ready for use outside of controlled clinical trials. The reasons are explained in the article, but not in most news reports.

The Purpose of the Trial

The goal of this trial is to see if it is possible to maintain HIV suppression with a reduced amount of antiretroviral drugs, in order to reduce toxicity and cost. There is no effort in this study to improve the treatment by allowing some return of the virus in order to stimulate the body's immune system against it.

Instead, this trial started with the observation that when HIV is very well suppressed by antiretrovirals, and the treatment is interrupted, it usually takes 2-3 weeks for detectable virus to return. Since there is so little HIV replication in that first week (assuming, of course, that the virus had been very well controlled when treatment was stopped), there should be little chance for the virus to develop resistance in that first week off the drugs. Then the treatment would be started again, keeping the virus suppressed. So far it seems to be working in this 10-patient proof-of-concept trial.

Cholesterol decreased 22% in this study, and triglycerides decreased 51%, after 24 weeks of intermittent treatment -- probably because patients had less exposure to the drugs. The researchers do not expect much change in lipodystrophy, however.

Comment: Why It's Not Ready to Use

We are concerned that people may start trying treatment interruptions without medical advice, in cases when it is entirely inappropriate for them. Here are some facts to consider:

* First and most important, all the volunteers in this trial had very well suppressed virus before they began. Viral load had to be below 500 copies for more than six months, and below 50 copies when they started the trial; also, they had to have a CD4 count of greater than 300. If someone tried this intermittent schedule when their virus was not suppressed, the whole idea of this trial would not apply. Instead, the frequent interruptions would cause periods of inadequate drug levels while the virus was replicating -- excellent conditions for the development of viral resistance.

* Also, all the volunteers in this trial received a four-drug regimen "selected to provide potent antiretroviral therapy with a high genetic barrier to the development of drug resistance" -- d4T, 3TC, indinavir, and a small dose of ritonavir (mainly to keep the indinavir in the blood longer). As an extra precaution, the last dose of ritonavir before each treatment interruption was not given, in order to clear the indinavir from the body faster.

* In addition, a research study can test viral load and other blood levels frequently, to detect treatment failure. Once a patient waited only three extra days to resume treatment (10 days instead of 7), and as a result had a viral load of over 3,000 copies. He was able to continue the study and regain viral suppression, but this case illustrates that control of HIV with this treatment schedule may leave little room for error.

* We still need to know whether this schedule works in longer-term use, whether it works in more advanced patients, and whether it can be used with other antiretroviral regimens. But the proof-of-concept trial suggests that when more is known, intermittent treatment might significantly reduce both cost and toxicity of antiretroviral therapy, and help to make it available in developing countries where cost is a major obstacle.

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AIDS and Hepatitis News from ICAAC Conference: Phone Overview, Web Reports

A one-hour review of the most important AIDS and hepatitis news at the 41st Conference on Antimicrobial Agents and Chemotherapy (ICAAC, Chicago, December 16-19) is available without charge through a toll-free phone number. You can hear a recording of a one-hour teleconference with leading experts, which took place in the evening of December 18.

To hear the recording, call 800-428-6051; when asked to enter a code, it is 212440. No registration is required.

This teleconference was organized by HIVandHepatitis.com, with unrestricted educational grants from Roche Laboratories, Inc., and Bristol-Myers Squibb Corporation.

Web Reports

Original written reports are being posted on several Web sites, including:
http://www.thebody.com
http://hiv.medscape.com/ (one-time registration required, but it's quick and free)
http://www.hivandhepatitis.com
http://www.natap.org

Also, you can find the official site through www.icaac.org -- select "Annual ICAAC", then select "Program and Abstracts online" for the 41st ICAAC (the 2001 conference). You will need to give your email address and choose a password to use this site. There is plenty of AIDS-related information; for example, a search for 'HIV' in the abstract text returns almost 200 abstracts. You might need to create an "itinerary" to view the abstracts; if so, the software can be confusing.

HIV Testing 101 (Part 2 of 2)

by Bruce Mirken

[Note: Part 1 of this article appeared in *AIDS Treatment News* #374, November 23, 2001.]

Detecting Acute HIV Infection

Shortly after getting infected with HIV, many patients have an acute (or "primary") HIV infection, a period of flu-like illness with symptoms like fever and malaise that could be caused by influenza or many other diseases. Many scientists and physicians believe it is important to treat during acute this HIV infection (provided, of course, that it gets diagnosed then). But there are still questions remaining about treating acute infection.[1,2]

To confirm an acute HIV infection in symptomatic individuals with potential HIV risk factors, current guidelines[2] recommend use of HIV RNA (viral load) tests. [The regular HIV antibody test will not detect acute HIV infection because the patient is still in the "window period" before antibodies have been produced.] False positives can occur with viral load tests, but a review of the data in the August, 1999 *American Family Physician*[1] suggests it is usually possible to differentiate these from the real thing: “During the symptomatic phase of acute HIV infection, the viral RNA shows in excess of 50,000 copies per mL. Three instances of false-positive HIV-1 RNA tests have been reported; in each instance, however, the person was not having symptoms and the viral load [reported] was less than 2,000 copies per ml. The presence of high-titer HIV-1 RNA (more than 50,000 copies per mL) in the absence of HIV antibodies establishes diagnosis of acute HIV infection.”

At present there is no viral load test approved by the FDA for the purpose of diagnosing HIV infection in individual patients. In September the FDA did approve a viral load test developed by National Genetics Institute for screening large pools of donated blood plasma.

If viral load testing is not available, current treatment guidelines[2] recommend testing for p24 antigen, a viral protein. In either case, the diagnosis should be confirmed by antibody testing once the window period has elapsed.

"Detuned" ELISA

A variation of standard antibody testing, presently approved in the U.S. only for research, is the sensitive/less sensitive or "detuned" ELISA. The detuned test takes advantage of the fact that antibody levels rise in a predictable pattern during roughly the first four to six months after infection, eventually reaching a plateau that often stays roughly constant for many years.

Current ELISAs can detect relatively low levels of antibodies. The detuned testing approach involves taking samples that are confirmed HIV-positive by these tests, but then retesting them with a less sensitive, diluted ELISA. This less sensitive test can only detect antibodies at the higher levels achieved during the period six months or more after infection. Thus, the detuned approach distinguishes between recent and established infections, so it is a potentially valuable tool for epidemiologists trying to chart the pattern of new infections. It is not used in patient care at this time.

Accuracy of Antibody Testing -- and Denialist Arguments

Constantine[3] sums up the general consensus among experts and institutions such as the CDC when he says "The antibody tests are nearly 100 percent sensitive (unless a person is in the window period) and about 99 percent specific." Such levels of accuracy have been documented in a number of studies, including periodic evaluations of commercially available test kits conducted by the World Health Organization.

Still, AIDS denialists (the self-styled "AIDS dissidents" who claim that HIV is either harmless or doesn't exist) continue to claim that HIV antibody tests are unreliable. Many of their arguments seem to derive from a series of articles written by Christine Johnson in the mid-1990s, several of which are available on denialist web sites.[4,5,6]

Johnson's argument boils down to two key points: 1) HIV has never been properly isolated, so the HIV proteins used in the tests haven't been proven to actually come from HIV, 2) Even if HIV is real, the proteins are not unique and cross-react with many other antigens, rendering a positive result meaningless. Johnson's list of some 60 factors she describes as "known to cause false-positive HIV-antibody test results" turns up regularly in denialist literature.

The claim that HIV has never been properly isolated, based on the writing of a group in Perth, Australia, is too technical and complex to examine thoroughly here. However, it is elegantly demolished in Michael Coon's article, "HIV, AIDS and the Distortion of Science," available on the AEGIS web site.[7] In short, Coon argues that the Perth Group set up artificial, phony criteria for "proof" of HIV's isolation that bear no relation to how virology works in the real world.

The second argument, though, contains a grain of truth. Cross-reactions are possible, and a number of factors can, on occasion, produce false-positive HIV antibody test results. What Johnson fails to address in any detail is that such effects are typically transient and rare, affecting few individuals.

For example, one well-known causes of false-positives Johnson lists is influenza vaccination. [8,9] But she neglects to mention that a key reference she cites described the phenomenon as "infrequent" and "of short duration," while in another only 10 false-positives were found among 133,000 individuals who had flu shots prior to testing, with half of those reverting to negative within six months.[9]

Constantine adds, "I doubt very much that it

has been firmly documented that 60 factors can interfere with antibody tests. In fact, it has been long sought to try and identify the causes of false positive results, and only a few have really been documented to consistently interfere (e.g. pregnancy, certain autoimmune diseases, some infectious diseases). However, even these do not consistently cause problems with the tests... There are very few false positives that can't be resolved with further testing."

Consent, Anonymity, and Counseling

(1) Anonymous Testing

Prior to HIV, blood testing was considered a routine procedure, with such minimal dangers that formal informed consent was rarely required. But because HIV presented massive psychosocial risks, from employment discrimination to rejection by family and reduced access to health care, special procedures were widely adopted.[10] These included specific informed consent and pre- and post-test counseling. Many states set up test sites where people could get tested anonymously, without ever giving their name.

Anonymous testing (other than the home test, below) was never universally available, Morin notes, but was and is offered in many places, despite the recent move by numerous states to adopt a system of names-based HIV reporting (a few, including California, are implementing HIV reporting via codes that don't reveal the person's name). The CDC and others urged that the option for anonymous testing should be kept available, believing fear of disclosure would keep some from being tested, and most states have followed this recommendation.

Because local laws and procedures vary, Morin recommends that anyone concerned about anonymity or disclosure contact their local health department to check. A number of AIDS service organizations operate hotlines, which should also be able to provide this information.

Those living in areas with no anonymous test sites can still be tested anonymously via home collection test kits, which are sold in many drug stores. Introduced in the mid-'90s, the kits were controversial because counseling is provided by telephone rather than in person. Morin says fears that telephone counseling would prove inadequate haven't been borne out, but sales of the kits have been less than expected. Still, "the FDA ruled that you cannot bar their sale in any state, so even in states that don't have anonymous testing people can use home test kits to anonymously be tested," he says.

But, he adds, things change when the individual seeks treatment: "If you go to your doctor and the doctor does a viral load test, you get reported through the viral load test to the health department. So there's no way to keep treatment for HIV anonymous."

(2) Consent and Counseling

As with anonymity, requirements for consent and counseling vary from state to state. Most, but not all, states require specific informed consent -- sometimes in writing -- for HIV testing. Approximately one-fifth of states require pre-test counseling, with many listing specifically what that counseling must include. The U.S. Department of Health and Human Services recommends that all HIV testing include counseling that covers the test itself, basic information about HIV and AIDS, how to avoid spreading the virus, the confidentiality of the results, the possible impact of the results on the person being tested, and discussion of to whom results should be disclosed, such as sex or needle-sharing partners.[11] Counselors should also be able to give referrals to medical and psychosocial support services.

Counseling and consent procedures vary greatly, remain controversial and may continue to change. Even states that require informed consent may allow HIV testing without consent in special circumstances. For example, many permit involuntary testing of a patient when

health workers have been exposed to the person's blood. Some test prisoners or people accused of sex crimes, and at least two, New York and Connecticut, require mandatory testing of newborns, which indirectly reveals the mother's HIV status, but does not tell if the infant has been infected.

In October 2000 the Institute of Medicine recommended that HIV testing be included as a routine part of prenatal care. Women would be informed of the test and could opt out, but specific consent would not be required. Thus far the U.S. Public Health Service has stopped short of urging an end to informed consent in such cases, simply suggesting that providers recommend HIV testing to all pregnant patients.

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AIDS Treatment News New Publication Schedule

by John S. James

AIDS Treatment News has traditionally published 24 issues per year. But in 2001 we ran behind and will only publish 19 issues. All current subscriptions have been extended so that subscribers will receive the number of issues paid for.

Starting in 2002 we are changing our publication frequency -- from twice monthly to 18 issues per year. We may publish more than 18 issues, and if so we will extend subscriptions to cover the full year.

Enough news is happening today to fill several newsletters, and we could easily write 24 issues per year. The problem is information overload. Because so much work is being done now, there is more background and context that reflects on the importance and credibility of research findings and other news. The most important reporting today will need time for investigating and understanding this background.

Notes:

(1) If your organization needs the subscription to begin in January, or at another time of year, let us know so we can prorate the billing to set the correct starting date.

(2) If you have already received an individual renewal notice at 24 issues per year, it will be accepted for 24 issues through January.