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Researching Alternatives

A Talk with Donald Abrams

By Bob Huff

You have a reputation as being a rigorous clinical researcher and tough advocate for making evidence-based treatment decisions. Yet you've also been very open to studying a number of alternative and complementary therapies that have been used in the HIV patient community. How did all these concerns come together and what are you involved with these days?

I was training in oncology at UC San Francisco just as the first AIDS cases were reported. I helped found the AIDS program there and I've been participating in academic clinical research for over 20 years. More recently I've become an associate fellow of the Program in Integrative Medicine at the University of Arizona that was founded by Andrew Weil. This is a two-year program, mostly online, that is increasing my training and background in integrative medicine, including things like botanical medicine, manual medicine, and spirituality. It's been a stimulating experience so far and I'm really enjoying it.

My intention is to continue to investigate the complementary and alternative approaches that our patients use.

I've been interested in complementary medicine since the very beginning of my career, so one of the reasons I'm doing the fellowship is to learn more that I can integrate into my own healthcare discussions with my patients. Of course another impetus is to see what other things we might want to do clinical research on. My intention is to continue to investigate the complementary and alternative approaches that our patients are using. We want to determine whether or not they may be beneficial, but also determine whether or not they may be harmful, particularly in how they interact with the conventional medications that patients are taking.

In the earliest days of AIDS we didn't have any treatment for this new disease; people were dying and everybody was frightened. Being here in San Francisco, we were near the Linus Pauling Research Institute in Palo Alto, so there were a number of people in the city who were proponents of high doses of Vitamin C. One of the first responses we saw in the early 80s were storefront clinics opening up where people went to receive intravenous injections of very high doses of Vitamin C. At that point in time we didn't even know that it was a virus causing the disease. So I used to go around on the lecture circuit with someone who would talk to audiences of concerned people who listened to him while hooked up to intravenous infusions of Vitamin C. Then I would speak as the academician who cautioned people that we really don't know if this is beneficial and there may be some dangers to being hooked up to intravenous vitamin C, and so on. Ultimately, this led to me to write a grant proposal

in collaboration with the Linus Pauling Institute. It was right about the time we learned that HIV was the cause of AIDS so we wrote a proposal to the NIH to study the in vitro effects of Vitamin C on HIV. That grant didn't get funded.

In San Francisco at that time there were also a number of DNCB proponents. DNCB, dinitroclorobenzene, is actually a photographic chemical used for developing pictures, but it is also a skin sensitizer that had been used to test for delayed hypersensitivity reactions. There were people who believed that somehow it might be useful in restoring some of the T cell immunity that patients with this new disease were lacking.

For thousands of years, people have depended on botanicals. As an oncologist I know that many of my most potent chemotherapeutic agents were derived from plants.

So there were people who would paint themselves weekly or so with DNCB until they developed these skin reactions, thinking that the skin reaction was some sort of improved T cell immune response that would help combat the virus. And again, seeing that people were using this and seeing that we really didn't have much else happening, I worked with some of the DNCB proponents, as well as some experts from the University of California — I remember Jay Levy was involved, as was Marcus Conant and others—and we wrote a protocol that we submitted to the FDA for funding. That also was rejected.

Around the time that AZT first became available in 1986, I went to a conference in Japan where I was introduced to some investigators from the Ueno Fine Chemicals company who told me that they had the cure for this disease. They said it was something that was very commonly used in Japan but they couldn't tell me about it until I signed a confidentiality agreement. That turned out to be dextran sulfate. Not long after I was going through the process of filing the paperwork to get approval from the FDA to do a phase I study of dextran sulfate in the United States when evidently some people heard about it. They realized that it was a product that was widely available in Japan — I believe it was used for lowering cholesterol—so they started an importation scheme similar to what had happened in earlier days with isoprinosine and ribaviran, which were brought across the Mexican border. But people had now become more sophisticated in their methods and began to import dextran sulfate from Japan to sell in the underground AIDS therapy market. I remember that activists stormed the offices of a Japanese drug distributor in New York for refusing to make dextran sulfate more widely available. Ultimately it became such a political issue that, even though my clinical trial here in San Francisco didn't show much benefit, Congress got involved and the AIDS Clinical Trial Group (ACTG) was asked to do a study of dextran sulfate through the NIH-funded mechanism. It turned out the drug was not even absorbed into the blood.

Another Japanese product I worked with was lentinin, which was an intravenously administered extract of shiitake mushroom. In Japan it was felt to be an immune booster for patients with cancer. Although it was being used by mainstream doctors in Japan, it was an alternative therapy here because it was not something that we had ever learned about or used in hospitals in the U.S. That's David Eisenberg's description of what an alternative therapy is—that it's not taught about in medical schools or widely available in U.S. hospitals—and certainly shiitake mushroom extracts qualified. Again, that's another study we did that had negative findings; there was no benefit to the intravenous infusions of lentinin. Since I've learned more about botanicals, it would seem to me that if there were immune enhancing benefits to shiitake mushrooms then they are more likely to be obtained by eating them rather than by injecting an extract intravenously.

During that time I was also involved with studies of conventional therapies. Even in the days of early AZT monotherapy, which I was not a big supporter of, I was involved in trying to put some evidence behind the claims of the proponents for these various agents. And since that time, I've had a constant history of investigating conventional therapies through the federally-funded CPCRA (Community Programs for Clinical Research on AIDS), and more recently through the ESPRIT study of interleukin 2, as well as in other, sometimes pharmaceutical industry-sponsored trials. But always ongoing with those studies, I've been involved with clinical trials of complementary and alternative interventions.

When we first became aware of immune thrombocytopenic purpora (ITP) in AIDS, I worked with a nurse who was very interested in therapeutic touch and we studied men with low platelet counts to see if therapeutic touch could decrease their stress and increase their platelet counts. That was another study that turned out to be fairly negative.

I then became interested in traditional Chinese medicine (TCM) and, in fact, one of the colleges of TCM here in San Francisco sent me to China in 1989 just to learn about Qigong (Chi Kung)—that exercise that's felt to improve the immune system—to see if it was something that I wanted to study here. Although I never studied Qigong I collaborated with Misha Cohen from

the Quan Yin Healing Arts Center here in San Francisco. We did three studies of traditional Chinese herbal interventions for, first, symptomatic HIV, then for patients with diarrhea without a pathogenic source, and then another study for patients with anemia. The last two were hindered by the fact of being initiated about the time that HAART became available, so patients with diarrhea as well as anemia became scarce. There were also a lot of pills that needed to be taken in these Chinese herbal investigations and patients at that time were taking huge amounts of pills with their antiretroviral regimens, so the studies weren't very attractive. None of these studies had spectacular results and the anemia study was terminated for poor enrollment.

Have "soft endpoints" such as life satisfaction created a problem for designing and conducting credible studies?

The TCM herbal study that we published in 1996 investigated herbs versus placebo in symptomatic HIV infection. At the time of the study in 1993, we had patients with about 14 symptoms on average and we found that there was a significant decrease of symptoms in the herb-treated group—they decreased from 14 to 12—whereas the other group still had 14 symptoms. We also found that they had improved "life satisfaction" which improved by a factor of +0.86 or thereabouts. Yet, if you look at the rest of the results, the Chinese herbal patients actually lost weight over 12 weeks compared to the placebo group, and their CD4 counts also dropped—not statistically significant, but it was a trend. So that was an example of where their symptoms improved and their life satisfaction increased, but the parameters that we would normally look at to see if a patient is doing well, i.e. weight and CD4 count, went in the wrong direction. So, although I was also first author on a study that showed that epoetin alfa improves quality of life in HIV patients who are anemic, I'd have to say that a study whose main endpoint is quality of life is something I would find difficult to interpret.

The CPCRA actually did a large study of acupuncture for patients with HIV-related peripheral neuropathy that was published in *JAMA*. That was a landmark, having the NIH support an acupuncture study, although, again, it turned out to have negative results; acupuncture didn't appear to be effective in treating peripheral neuropathy.

About this time I began trying to study another botanical, which has consumed my efforts for the past decade, and that would be cannabis, or marijuana. Starting in 1992 I began proposing and developing clinical trials to investigate first the effectiveness—but then I realized that that wasn't going to happen—so subsequently, the safety of smoked marijuana in patients with HIV. We finally completed a study in the year 2000, that we hope will soon be published, that looked at the safety of marijuana in patients taking protease inhibitor regimens. And since that time we have obtained funding from the State of California that allows us now to conduct clinical trials to look at the potential effectiveness of smoked marijuana in patients with various syndromes. We have also just completed a pilot study in patients with HIV peripheral neuropathy, which allowed us to ascertain that there was some effectiveness of marijuana. But an open-label pilot study is not going to prove that, so we're now in the process of continuing on with a randomized, placebo controlled, double-blind trial in patients with HIV-related peripheral neuropathy. We're also doing marijuana studies in patients with cancer who have pain who are on opioid analgesics, and another study to look at the effect of smoked marijuana in patients who have delayed nausea and vomiting from breast cancer chemotherapy.

We completed a study in 2000 that looked at the safety of marijuana in patients taking protease inhibitor regimens.

It was working with marijuana and all the problems that are inherent in studying a plant as a therapy that has led me to a broader interest in botanicals and the use of substances that come from nature as medicinal agents. Certainly, for thousands of years, people have depended primarily on these things. Whether or not they worked is unclear, but as an oncologist I know that many of my most potent chemotherapeutic agents were derived from plants. So right now we are waiting to hear if a protocol we submitted to the National Center for Complementary and Alternative Medicine (NCCAM) to investigate the lipid lowering effects of oyster mushrooms in patients on Kaletra is being funded. There's good evidence that mushrooms, including oyster mushrooms in particular, have some activity for lowering blood lipids and cholesterol.

We're also just finishing a three-year NCCAM grant studying the effects of DHEA, dehydroepiandrosterone, which is an over-the-counter adrenal steroid that people are taking for many reasons. We received a grant to investigate it as an antiviral and to see what impact it has on the immune system. Hopefully that data will be available by the end of the year and we will know if DHEA had any impact, positively or negatively, in our patients.

The goal, ultimately, would be to submit a center grant to the NCCAM, to allow us to

establish a center here for the study of botanicals in HIV because there are still a number of herbal preparations and mushroom extracts that warrant further investigation for their potential benefit—and to make sure that they're not harmful in our patients.

Safety keeps coming up again and again as one of the inarguable justifications for doing this research.

There's not a huge amount that we know about some of these botanical products and how they're metabolized, but there's probably more than people think. There are a number of textbooks available that talk about herb-drug interactions. That was the question in our marijuana study: is there an interaction between cannabinoids and protease inhibitors, which are both metabolized by cytochrome P450 enzymes in the liver, that may alter the activity of the protease inhibitors such that patients lose their viral suppression when they mix cannabis with their treatments? And in fact, in our article that was already published in *AIDS*, we saw no such effect. We've all heard about garlic and St. John's Wort and their interactions, and I think there are many other agents that we would like to study to make sure that they are not having significant interactions with protease inhibitors. We don't want people to either lose control of their viremia (through underdosing) or experience toxicity (through overdosing) because of antiretroviral concentrations that have been affected by herb-drug interactions.

Patients don't really perceive that these substances are something that they need to tell their doctor about. And many physicians never think about asking.

You had to be enormously persistent to accomplish your marijuana study. In the current political climate, is it going to be more difficult to do marijuana studies?

I think we're blessed to live in the State of California, which is somewhat of a freestanding republic in and of itself. In 1996, the people of California voted to allow physicians to talk to their patients about the medicinal use of cannabis. Then, through the work of Senator John Vasconcellos, one of our state senators, appropriations were made to the University of California that established the Center for Medicinal Cannabis Research (www.cmcr.ucsd.edu). And that Center has had funds for the past three years that allows it to support clinical trials to investigate the use of marijuana for medicinal purposes. Whereas the NIH and NIDA, via their congressional mandate, could only give marijuana to clinical trials that show that it was harmful (they are the National Institute on Drug Abuse, not for Drug Abuse, as NIDA's director Alan Leshner always reminded me), they were not really able to provide us with marijuana to study the benefits. But now, they have modified their system so they can provide marijuana for peer reviewed clinical trials that will look at its effectiveness as a therapeutic agent—as long as they are not funding it. So they have now created this ability for us to obtain government marijuana.

Is there a need to increase provider knowledge about these issues?

I think a part of the problem is a lack of communication from both sides. Patients don't really perceive that these substances are something that they need to tell their doctor about—in fact many studies show they don't want to tell their doctor because they're afraid they're going to be reprimanded or told that they're wasting their money. And many physicians never even think about asking about these things as potential confounders or as things that are causing clinical symptoms. There also may be a variable of where in the country you are. I know many surveys show that we in the West have the highest percentage of people in the population who are using complementary and alternative interventions. So many of my colleagues here might be more familiar with how to ask the question and what to be looking for.

I remember once seeing a patient at our drop-in clinic who clearly had a drug rash. I looked through his chart—this was when we had paper charts—and he had a high CD4 count and a low viral load but he wasn't taking any medications.

So I said to the guy, "You're not taking any medications, huh?" And he said, "No."

"Are you taking any vitamins?" And he said, "Yeah."

So I asked him what he took and he listed about four or five vitamin preparations.

Then I asked, "Do you take any herbs?" And he said, "Sure."

And so I listed the three or four herbal substances that he took.

"Do you take any minerals?" And he said, "Yeah."

By the time I finished I had a list of 12 different things he was taking.

So I asked, "Well, how come everybody else wrote down that you don't take anything?" And he said, "Well, nobody ever asked me before."

"Alternative" Treatment Activism

By Jon Greenberg

A version of this article originally appeared in Treatment Issues *in the Winter of 1993/94. It was edited posthumously from the writings of Jon Greenberg, who died of AIDS on July 12, 1993.*

Since the beginning of the AIDS crisis, a number of "alternative" medical treatments have been proposed and used with unknown success, such as herbal compounds, nutritional supplements, traditional Chinese medicine, as well as physical manipulation techniques and spiritual approaches. Although these methods have all been lumped together under the generic category "Alternative or Complementary Health Care," they differ substantially in philosophy, modality, cost, and other important ways. However, they all share one unfortunate similarity—virtually nothing is objectively known about their activity in the human body and their efficacy for treating HIV/AIDS.

The AIDS community tends to fall into two separate camps regarding alternative therapies. Some dismiss all alternative treatments, regardless of evidence that demonstrates efficacy, while others defend all alternative therapy, regardless of evidence suggesting toxicity or lack of benefit. The reality probably lies somewhere between these two extremes; some alternative therapies may be effective, some are clearly ineffective, and most possess some potential for toxicity. The chief difficulty with using alternative therapies is a lack of empirical data and an absence of commercial scientific interest in these compounds. Presently, there is no research infrastructure to systematically address the potential benefits and risks of alternative treatments using controlled experiments, the most rigorous known method of producing convincing data about a treatment's effects. Every FDA approved medicine for HIV has gone through this process. Why not study all the treatments that people with HIV use in the same way?

Obstacles to Testing Alternative Therapies

One goal of alternative therapy activists should be to advocate for controlled clinical trials of alternative treatments, so that people can make informed decisions about using them and that wider acceptance can be gained for those treatments that are found to be effective. Our goal should be to make the term "alternative" obsolete. At present, very few alternative treatments are ever studied in a government- or university-sponsored clinical trial. They have never gone through a process that details their toxic effects in humans; assesses bioavailability, pharmacokinetics, safety and efficacy; or determines their impact on the immune system.

Since toxicity studies on most alternative therapies have not been conducted—and since some alternative treatment practitioners may recommend these therapies at very high doses—it must responsibly be asserted that toxicities may occur. Yet, for the most part, if a proponent of a specific alternative therapy has observed negative side-effects, there is no mechanism, no mandate, no regulation, and therefore no institutionalized reason to disclose such information. And, of course, profit can be as big a motive for the "alternative" medical community as it is for the conventional pharmaceutical industry.

Believing that only doctors and orthodox medicine holds the answer can be an obstacle to the self-empowerment of people with HIV.

Even when alternative treatment proponents have no financial investment in proposed therapies, the emotional investment in the therapy's success is usually high. Many alternative treatment enthusiasts have a strong desire to prove conventional Western medicine wrong. This sentiment sometimes precludes objective evaluation. Very often, claims of efficacy and recommendations for alternative therapies are based on anecdotal reports or loosely designed observational studies. Design flaws, poor execution, or too-limited sample size prevent these studies from generating useful or reliable information.

Making Decisions in the Information Vacuum

It is tiresome and sometimes confusing to depend on other people's stories in order to make treatment decisions. As we all know, these stories are often colored by biases and histories that we may not necessarily share. This is not to say that these personal experiences are invalid for those who believe and promote them. But each of us has a different biological, emotional, historical, psychological and intellectual make up.

Every person with HIV uses a variety of methods to gather information on treatment options. How much do I take? How often do I take it? Is it a pure substance? What are the possible side effects? Will it work? This decision-making process is complex and individual. We are too often forced to make decisions without much information. Unfortunately, getting the

information we need may require a long process. And even controlled clinical studies of alternative treatments, although necessary to gather scientific information, may ultimately yield little useful information. Quite frankly, results from controlled clinical studies often raise as many questions as anecdotal reports or personal histories do.

Health care practitioners who share questions, doubts, criticisms about treatment (as well as beliefs in a particular therapy), can help people with HIV most by encouraging patients' responsibility for his or her own decision-making process. People with HIV also need to know that doctors do not have all the answers and that much of the information they use to make treatment decisions can be learned. Believing that only doctors and orthodox medicine holds the answer can also be an obstacle to the self-empowerment of people with HIV. Ideally, the trust in a treatment decision should come from within.

Taking Action

It is important to identify through controlled clinical studies those treatments that seem most promising for potential development. We must make contacts among key researchers in pharmaceutical settings, the federal government, research universities, and institutes across the country. (In pursuing these issues, I've found it easier and more expedient to speak the language of the researchers and the scientific community than it is to force them to speak the language of people with AIDS and alternative treatment activists.) We must create an interest in the research establishment to address the obstacles to research on alternative treatments. We must learn how to write concept sheets, the blueprints for clinical trials designs, to spark the interest of researchers. We must strategize the best way to study the compound in question and the most politically efficient manner to initiate study. This often involves writing letters, making phone calls, and staging political actions to urge all the parties involved to take action. We need to get their attention.

Controlled clinical studies may offer the only opportunity to directly evaluate alternative treatment options using well-defined criteria. We should not have to place extraordinary faith in one practitioner or theory of disease and treatment, whether conventional or alternative. We need answers to our questions.

Moving Forward with Integrative AIDS Research

By George M. Carter, Mark Kuebel and Evan Ruderman

The Foundation for Integrative AIDS Research (FIAR) is a not-for-profit organization formed in October, 2001, to sponsor and stimulate interest in clinical trials of herbal and nutritional treatments for people with HIV, AIDS and chronic hepatitis. The goal is to show whether or not these treatments can lessen symptoms, delay the use of Western drugs, reduce side effects, and are safe. FIAR is working to develop studies in developing nations where indigenous treatments are used and Western drugs are largely unavailable. FIAR also seeks to help bring affordable Western drugs, education and prevention to such under-served areas.

FIAR has been working on several studies in collaboration with the Mt. Sinai Medical Center. Among these are a study of milk thistle in people with HIV and hepatitis C, a study of the Ayurvedic herb, Bacopa monniera for minor cognitive motor disorder, and a proposed phase I study of a therapy being used by Siddha practitioners in Southern India. Siddha is an ancient traditional medicinal system of India. FIAR has also started a pilot condom distribution program for men who have sex with men in Kathmandu, Nepal, working with the Blue Diamond Society. Groundwork is being laid for an STD/HIV clinic there.

The goal in working with local communities is to design and implement clinical studies that help establish and strengthen local capacity by bringing attention and funding where it is needed. FIAR's selection of clinical questions to be addressed will be drawn first from the infected and affected community. Such a grassroots based approach to generating study questions will help promote a sense of cooperation and comradeship between researchers and people living with disease. Of course, the first duty to participants in such studies is to assure only the highest standards for informed consent, patient protection and careful monitoring are met.

It's time that people had better information to help guide treatment choices. Many studies show that a high percentage of people living with HIV/AIDS already use many of these interventions. Yet many questions remain: How do they work? Can they help to manage side effects of drug therapy? Can they slow the rate of progression? FIAR, working with the HIV/AIDS and Hepatitis communities, clinics, hospitals, practitioners and organizations around the United States and elsewhere, intends to design, fund and implement clinical studies to address some of these questions and thus help people make better-informed treatment decisions.

For more information about FIAR: E-mail: fiar@verizon.net. Web: http://aidsinfonyc.org/fiar

HIV/AIDS and People with Disability

By Nora Ellen Groce

Reprinted from The Lancet, *April 26, 2003*

Although AIDS researchers have studied the disabling effects of HIV/AIDS on previously healthy people, little attention has been given to the risk of HIV/AIDS for individuals who have a physical, sensory, intellectual, or mental health disability before becoming infected. It is commonly assumed that disabled individuals are not at risk. They are incorrectly thought to be sexually inactive, unlikely to use drugs, and at less risk for violence or rape than their non-disabled peers. Yet a growing body of research indicates that they are actually at increased risk for every known risk factor for HIV/AIDS. For example, in a recent article, S. Blumberg and W. Dickey analyze findings from the 1999 U.S. National Health Interview Survey and show that adults with mental health disorders are more likely to report a medium or high chance of becoming infected with HIV, are more likely to be tested for HIV infection, and are more likely to expect to be tested within the next 12 months than are members of the general population.

Such findings should not be unexpected for individuals with disability. There are significant risk factors for disabled populations around the globe. For example, despite the assumption that disabled people are sexually inactive, those with disability—and disabled women in particular—are likely to have more sexual partners than their non-disabled peers. Extreme poverty and social sanctions against marrying a disabled person mean that they are likely to become involved in a series of unstable relationships. Disabled individuals (both male and female) around the world are more likely to be victims of sexual abuse and rape than their non-disabled peers. Factors such as increased physical vulnerability, the need for attendant care, life in institutions, and the almost universal belief that disabled people cannot be a reliable witness on their own behalf make them targets for predators. In some countries, parents of intellectually disabled children now report rape as their leading concern for their children's current and future well-being. Individuals with disability are also at increased risk of substance abuse and less likely to have access to interventions. It is estimated that 30% of all street children have some type of disability and these young people are rarely reached by safe-sex campaigns.

Furthermore, literacy rates for disabled individuals are exceptionally low (one estimate cites an adult literacy rate of only 3% globally), thus making communication of messages about HIV/AIDS all the more difficult. Sex-education programs for those with disability are rare, and almost no general campaigns about HIV/AIDS target (or include) disabled populations. Indeed, where AIDS campaigns are on radio or television, groups such as the deaf and the blind are at a distinct disadvantage.

The future for disabled individuals who become HIV-positive is equally grim. Although little is known about access to HIV/AIDS care, disabled citizens receive far fewer general health services than others. Indeed, care is not only often too expensive for impoverished disabled persons, but it can also be physically inaccessible—e.g., clinic steps bar the way for a wheelchair user and consultation with a physician without a sign-language interpreter is meaningless for most deaf persons.

Currently, little is known about HIV/AIDS and disability. Only a few studies have estimated prevalence and no prevalence data exist for any disabled populations from sub-Saharan Africa, Asia, Europe, Central and South America, or the Caribbean. However, a growing number of stories from disability advocates worldwide point to significant unreported rates of infection, disease, and death. Over the past decade there have be a handful of articles on HIV/AIDS pilot programs and interventions for intellectually disabled adults or services for deaf adolescents. Many of these projects are innovative but almost all are small and underfunded. There is a real need to understand the issue of HIV/AIDS in disabled people in global terms and to design and implement programs and policy in a more coherent and comprehensive manner. The roughly 600 million individuals who live with a disability are among the poorest, least educated, and most marginalized of all the world's peoples. They are at serious risk of HIV/AIDS and attention needs to be focused on them.

In January 2003, the World Bank and Yale University, started a global survey on HIV/AIDS and disability that seeks to better understand variables of the current epidemic as well as to identify best-practice interventions and grassroots efforts.

Organizations that serve people with HIV and disability are invited to participate in the survey. International respondents are especially welcome.

Contact: Nora Ellen Groce, Global Health Division, Yale School of Public Health, Yale University, New Haven, CT 06520, USA; e-mail: nora.groce@yale.edu.

Reyataz Dosing Options Discussed

Excerpts from the FDA Atazanavir Hearing

By Bob Huff

Atazanavir has been developed as a once-a-day (QD) protease inhibitor to treat HIV infection in combination with other antiretrovirals. Its approved dosage will be 400mg QD, taken with food. The convenience of QD dosing is expected to enhance regimen adherence and contribute to treatment effectiveness.

Atazanavir (ATV) is distinguished among protease inhibitors by having little impact on blood lipid levels such as cholesterol and triglycerides. Patients who had developed high lipid levels after taking other protease inhibitors experienced normalization of lipids after switching to atazanavir. Atazanavir also had a unique and favorable resistance profile among protease inhibitor naive patients in which resistance, when it occurred via the protease mutation I50L, produced a virus with increased susceptibility to other protease inhibitors. A dose limiting side effect is the development of jaundice or yellowing of the eyes due to otherwise benign bilirubin increases in a large proportion of patients.

Boosting with ritonavir improved Cmin considerably. But there are unanswered questions about the compromising effect that adding ritonavir might have on the lipid benefits of unboosted atazanavir.

In a head-to-head comparison for 48 weeks, atazanavir performed as well as efavirenz for lowering viral load below the limits of detection in a large phase III clinical trial in people beginning their first anti-HIV regimens. However, in 24 week data from a trial in people with prior protease inhibitor therapy, 400mg of atazanavir QD did not perform as well as a standard dose of Kaletra. But when blood levels of a 300mg dose of atazanavir were boosted by 100mg of ritonavir (RTV), reductions of viral load after 24 weeks were equivalent to those produced by Kaletra in the treatment experienced population.

On May 13, 2003, an FDA antiviral advisory committee, a panel of experts convened by the federal Food and Drug Administration, met to discuss data submitted by Bristol-Myers Squibb (BMS) to support the approval of atazanavir. The daylong meeting considered issues ranging from possible cardiac effects to the type and quantity of "food" that should accompany a dose of atazanavir. Although data on the efficacy of ritonavir-boosted atazanavir for treating protease inhibitor experienced patients was shown at the meeting, it had not been received in time for evaluation by the FDA, and was not officially considered part of the sponsor's application. This created a quandary for the committee members who, while generally convinced of atazanavir's efficacy in a treatment naive population, felt that unboosted atazanavir for patients with prior PI mutations would not be a wise choice. They felt they had no alternative but to consider data about boosted atazanavir that had not been officially presented to them.

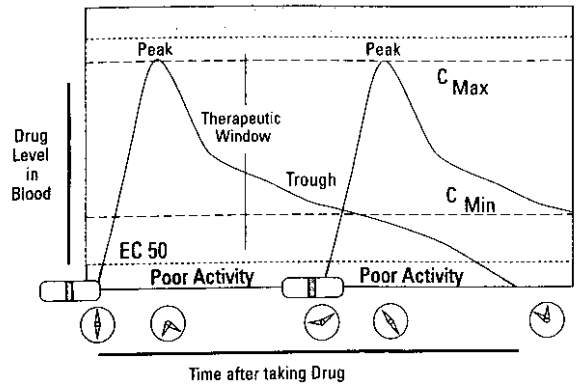
The following are edited excerpts from the hearing that focus on the issues of atazanavir blood levels at the end of a dose cycle (Cmin; minimum concentration) and the question of whether to support the approval of unboosted atazanavir knowing that in practice, it will likely be boosted with ritonavir in treatment experienced patients. Boosting with ritonavir improved Cmin considerably. There were also a few questions about the compromising effect that adding ritonavir to the regimen might have on the lipid benefits seen with unboosted atazanavir.

Despite the apparent effectiveness of 400mg atazanavir in treatment naïve patients, several committee members were concerned by data from pharmacokinetic (PK) studies that revealed wide variability in the Cmin at 24 hours. They questioned if subtherapeutic doses at Cmin in some treatment naïve patients were responsible for treatment failures seen in the Phase III study.

The significance of Cmin is acknowledged in this sentence from the sponsor's briefing document: "The association of Cmin with antiretroviral activity is consistent both with HIV being a continuously replicating virus, and with drug needing to be present at all times in concentrations that equal or exceed those concentrations required to inhibit viral replication."

The lower range of Cmin in atazanavir PK studies at 400mg QD was 12 ng/ml. The EC90 of atazanavir, the drug concentration observed to inhibit virion production by 90 percent in a cell-based assay, after adjustment for protein binding, was about 75 ng/ml against a laboratory strain of HIV. However, similar assays performed with actual HIV isolates from treatment naive patients produced a median EC90 of 14 ng/ml, with values ranging from 2.4 to 40.6 ng/ml.

It should also be noted that only 24 hour Cmins were reported. Data on 48 hour Cmin, such as might result from a skipped daily dose, were not presented.



Definitions:

Cmax: the maximum concentration of a drug in the body after dosing. It defines the peak level after dosing. Cmax is often associated with side effects.

Cmin: the lowest concentration of a drug after dosing. It defines the trough level at the point when another dose is taken.

EC50: A point half-way between a concentration of drug that produces 100% suppression of HIV in a laboratory test and one that produces no suppression. **EC90** reflects 90% suppression.

Pharmacokinetics (PK): the study of the absorbtion, distribution, metabolism and elimination of drugs in the body.

Therapeutic drug monitoring (TDM): measuring blood drug levels so that the most effective dosage can be attained with minimal toxicity.

Discussion

Discussants: Antiviral Drugs Advisory Committee Chair: Roy Gulick, MD, MPH; Members: Eugene Sun, MD, Rory Remmel, PhD, Courtney Fletcher, Pharm.D., Wm. Christopher Mathews, MD, Janet Englund, MD, Thomas Tephly, MD, Princy Kumar, MD. For FDA: Debra Birnkrant, MD. For BMS: Michael Giordano, MD, Steven Schnittman, MD.

A complete transcript of the FDA hearing can be found under "Antiviral Drugs" at: www.fda.gov/oc/advisory/acdrugs.html

On the Cmin in naïve patients:

DR. SUN (ABBOTT LABS): In your analysis of the virologic failures from your various clinical trials, have you analyzed the pharmacokinetics in those patients, especially given the fact that there is a fairly large variability in PK, particularly around Cmin (see Table 1), and that that might account for a substantial part of the failures that you can't attribute just to phenotypic analysis?

Table 1: Mean (Range) Steady-State Pharmacokinetic Parameters of Atazanavir

	ATV 400mg Unboosted	ATV 300mg/ RTV 100mg Boosted
Cmax (ng/ml)	5358 (3166-7970)	6450 (2829-11910)
Cmin (ng/ml)	218 (12-840)	1441 (214-3323)

DR. SCHNITTMAN (BMS): We have not selectively analyzed the pharmacokinetic parameters in those subjects who have failed. In fact, when one goes back and looks at these patients, many of the reasons for failure have to do with adherence, compliance or other issues that really have no bearing on what the actual absorption of drug is.

DR. REMMEL: At the 400 mg dose, clearly, there was good effect with atazanavir, but I am concerned about the pharmacokinetic variability of the drug.

While the sponsor probably wouldn't want to encourage concentration monitoring (TDM), this is a major issue in terms of many of the protease inhibitors, especially because they are all CYP3A substrates, and I think that we could see some benefit if it was to be done. But I would like to see some sort of indication of how many patients who fell at the low end for the Cmins or area under the curve were actually failing, and what that component is in terms of the efficacy of this drug.

DR. GULICK: Then, Dr. Remmel, you suggest maybe TDM would be an interesting thing to think about for this drug?

DR. REMMEL: It is not something sponsors like to hear, but I think that we can understand more about this drug (by doing TDM). (The drug) does have a very large variability in the PKs when it is not taken with a boosted ritonavir dose. Now, it may be overly burdensome for certain patients and certain types of practices, but I think from the company's standpoint, I would want to know where my trough levels are.

DR. GULICK: Dr. Fletcher, anything to add?

DR. FLETCHER: I would agree. I think as a Phase IV study, (TDM) would really be a worthwhile study to consider. It actually goes to Dr. Sun's question about what was the incidence of pharmacokinetic reasons for failure in patients, and if you look at the well-controlled pharmacokinetic studies that the sponsor presented, the range of trough concentration goes down to 12 nanograms per ml, which is below the adjusted IC50, and I think that has to clearly put a patient at risk of failure.

The best response is always to the first regimen. If there is an opportunity to improve the rates of response in naive patients, I would think

that would be good for patients and good for the sponsor to take a look at. So, I would encourage some serious look at whether therapeutic drug monitoring could improve response of patients to this drug.

What can the drug label say about atazanavir in treatment experienced patients?

DR. FLETCHER: This would be a question to the FDA. Would the agency consider, in the dosing recommendations, the use of the boosted atazanavir/ritonavir dose (300/100 mg regimen), or does the dosing really have to be constrained to the 400 mg, once daily, dose (supported by available data)?

DR. BIRNKRANT (FDA): As of today, it would be restricted to the 400 mg dose. The date by which a regulatory decision has to be made by law, is the 20th of June, so between now and then, there isn't that much time to review that additional data that came in late.

"We can't forget the advantage of the lipid-lowering quality of this particular agent."

DR. MATHEWS: There is a real dilemma, I think, facing the committee and the agency because the agency has not reviewed the 16-week data on the PK-boosted regimen, and yet the (unboosted) data that was reviewed in experienced patients (leaves a physician) with the decision of using a regimen which may have inferior virologic outcomes, but has a lot of advantages in terms of simplicity, tolerability, and so on.

Based on the data that is reviewed and reviewable at this point... you could say that it's superior to placebo based on the comparisons that were done in that trial, but inferior to a regimen containing Kaletra.

DR. GULICK: It puts us, as a committee, in an awkward position because we are seeing evidence of activity (in treatment experienced patients), but it is not as good as a comparator arm; at the same time, we saw preliminary activity which hasn't been reviewed by the agency, which seemed to suggest similar virologic effects to a Kaletra-based arm. In addition, (we also saw) pharmacokinetics data to support better drug levels and a better Cmin, when boosted with ritonavir, so I think that we are feeling a bit conflicted about this point.

DR. BIRNKRANT (FDA): Well, it is a dilemma for us, as well, to see snippets of data that look potentially promising, but given that it was submitted so late, it is difficult to review all of that data within such a short period of time.

DR. FLETCHER: Well, in my mind, (the boosted regimen data) is the only data that would really make the case for using the drug in the treatment-experienced patient. If you have to look at just the 400, once daily, regimen versus Kaletra, it wasn't as good as other available agents.

DR. GULICK: Other thoughts on that?

DR. ENGLUND: But I also can sense at least from the people I work with, and I know the FDA appreciates this, too, is the sense of urgency. We have patients that are running out of alternatives.

DR. GULICK: Other opinions about this? Dr. Mathews.

DR. MATHEWS: Let me say that I think we would not be well advised to take the extreme position of saying that because it's inferior to a Kaletra-containing regimen, it shouldn't be approved for treatment-experienced patients. I mean I have lots of patients who are having a lot of trouble taking Kaletra or other PI-based regimens that are very anxious to get to a simplified PI regimen. On the other hand, I am going to have to tell them, "You are barely controlled right now, and the small difference in efficacy between what you are on now and this more simplified regimen may cost you long-term virologic control. We don't know."

DR. GULICK: Clearly, the biggest need in the clinic right now is not so much the early failure people where you may have several options to choose from, but in the later stages where you want some good options. (The drug's benefits) in a naive regimen—low pill count, once a day, apply in the salvage setting, as well.

DR. REMMEL: There is, of course, another class of experienced patients to consider, and those would be patients who already have disturbed lipid profiles and who you want to switch to lower their cholesterol or lower their triglycerides especially. That clearly would be advantageous for many patients in addition to simplifying their regimen.

DR. TEPHLY: Exactly. We can't forget the advantage of the lipid-lowering quality of this particular agent.

DR. GULICK: Other comments on the experienced? Dr. Kumar.

DR. KUMAR: I want to echo some of the comments that Dr. Mathews had said. In the treatment-naive patient, I think it is an excellent drug, it's a drug that I feel very, very comfortable with, but in the treatment-experienced patient, using it by itself, with unboosted dose, my concern is that failure begets failure, and in that setting, despite its convenience, the dosing, that it may lead to the development of more and more resistant mutants, so that is really what I am concerned about, using it as a single dose of 400 mg without boosting.

DR. MATHEWS: I have a question about the (lipid) effects of boosted atazanavir compared to

unboosted: In one of the slides that Dr. Grunfeld showed, in experienced patients, the proportion taking lipid-lowering therapy on unboosted regimens was about 4 percent; boosted, it was 7 percent, which is nearly twice as much. So, I think it is relevant to know what the direct comparison is; how much of (atazanavir's lipid) benefit is lost if it's boosted?

DR. GIORDANO (BMS): We don't have data which is a head-to-head comparison of atazanavir boosted versus unboosted, so I can't answer that specific question. Sorry.

DR. GULICK: Let's shift gears and talk about what the resistance data implied about the use of atazanavir in experienced patients. We saw lots of evidence for cross-resistance in the highly PI-experienced patient. Maybe we could also think again about atazanavir by itself versus boosted atazanavir.

Dr. Fletcher, why would a ritonavir-boosted atazanavir regimen work better against a resistant virus?

DR. FLETCHER: Well, it's because of, to use the term from the sponsors, the PK cushion. You have an inhibitor that is going to raise the atazanavir levels, and in the case of viruses that have decreased susceptibility, it will provide the more typical type of relationship between the concentration of drug and the concentration that the virus needs to inhibit it.

DR. REMMEL: Again, I think this is where sometimes a pharmacokinetic evaluation could be helpful. If you had a 5-fold increase in resistance, and you have a patient with a longer half-life, you might feel more comfortable about raising the dose slightly to make sure that you have a good therapeutic window.

For patients with shorter half-lives, you feel like you can't reliably raise that window. Because of a 24-hour dosing interval, you could go to a more frequent dosing interval or perhaps go to a boosted regimen. We haven't really talked about giving the drug on a BID (twice-a-day) schedule, but many patients could adhere to that schedule, and that might solve some of those problems.

DR. MATHEWS: As I said earlier this afternoon, if you are trying to trade off toxicity, simplicity and lipid (benefits) with virological efficacy or effectiveness, having a more precise estimate of what the pharmacodynamic response pattern is in experienced patients is very important.

What post-approval studies should be considered?

DR. MATHEWS: I mentioned a study that I thought should be done: a direct comparison of boosted versus unboosted for the lipid effect, but perhaps that could be studied in the context of another naive trial of boosted versus unboosted atazanavir to improve on the long-term response rate, because, for whatever reason, 65 percent suppressed at 48 weeks is not optimal.

Commentary

The outstanding rationale for developing atazanavir for the HIV market has been once daily dosing. The clear consensus of the FDA advisory committee was that 400mg QD will produce adequate drug exposure for most treatment naive patients (resistance testing prior to starting a first regimen is recommended to assess susceptibility). For those with ARV resistance, that dosage was recognized as inferior to a ritonavir-boosted dose. Yet there were also concerns that the unboosted dose will not provide sufficient coverage in a minority of naive patients. Higher doses produced unacceptable bilirubin increases, and while boosting with ritonavir was effective at increasing Cmin without increasing toxicity, the important lipid-neutral benefits of atazanavir may be compromised—an unexplored issue for experienced persons, as well.

There is a real concern among community activists that QD dosing will be oversold in advertising for Reyataz. Since no information about the efficacy of a boosted regimen will appear on the product label, there will be a critical need for education to clarify the limitations of 400mg QD in treatment experienced individuals. For naive patients, discovering which are susceptible to low Cmin and would benefit from boosting, higher doses or more frequent dosing, may be a problem. Several committee members recommended TDM (therapeutic drug monitoring) of drug concentrations in the blood, a complicated assay that is not widely available in the U.S. Post-marketing studies of TDM to determine the frequency of low Cmin in the patient population should receive top priority.

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VOLUNTEER SUPPORT STAFF
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GMHC Treatment Issues
The Tisch Building
119 West 24 Street, New York, NY 10011
Fax: 212/367-1235
e-mail: ti@gmhc.org
www.gmhc.org

A Space and Time for Healing:
The Importance of the Abundance Paradigm

By Ana Oliveira

November, 1981, 7:30 A.M.; clients line up in front of an old Department of Health building in the Bronx—the acupuncture building. It was there I learned the vital importance of healing; of maintaining an environment that *holds* healing.

June, 2003, 12:30 P.M.; clients sit with eyes closed, quietly, in The Corner, the acupuncture space at Gay Men's Health Crisis. It is here that I learn the continued importance of long-term healing; of maintaining a space that *holds and integrates* healing.

The longer the AIDS plague continues, the more important it becomes to integrate and multiply the opportunities for access to complementary therapies in the lives of our communities. Whether through traditional healing practices received from ancestors, or through desperation and the need for alternative options, more and more individuals are using complementary therapies to support and enhance the quality of their lives. The increasing complexity of HIV medical management and its side effects, the increasing limits on access to care, and the growing toll of untreated mental health conditions compel us to recognize and institutionalize effective complementary therapies into all of our helping organizations.

Holistic and complementary therapies are increasingly being brought into public health settings in the U.S. Urban and rural substance abuse clinics, criminal justice and prison settings, emergency and crisis-intervention settings have all benefited from the immediate rewards and drug-free approach offered by holistic interventions. From nutrition to acupuncture to herbal treatments, more and more practitioners are motivated to practice in public health settings, reaching the neediest and most complex clients. Schools are bringing internships and off-site trainings to community-based organizations that facilitate access to the practitioners, interventions, and staff of holistic centers.

Complementary therapies use mostly non-verbal, non-intimidating methods and work well alongside other interventions. They tend to operate from a building, or re-building approach, as a teacher would, strengthening the capacities that are present and opening up a receptivity for change. They enhance, rather than decrease; they release, rather than control; and they can create experiences that are critical for the healing of individuals and of communities that are the most depleted and vulnerable. They build towards, rather than fight against, and in doing so generate the actual experience of hope and possibility that is so critical for continuing the fight in this plague.

Complementary therapies are also, relatively speaking, much less expensive than allopathic medicine. Because they attempt to integrate the spirit, the body and the mind, they tend to be less fit for simple marketplace solutions. The importance of the personal exchange and the relationship between the practitioner and the client creates an invaluable opportunity for energetic exchange and becomes a unique aspect of the healing encounter. Vulnerable communities and individuals often describe their access to complementary therapies as a strengthening experience and a necessary one for the improvement of their health. Some complementary approaches can be taught and can involve members of the family network, thereby enhancing the sense of competence and independence that is so critical for sustained healing.

Most importantly, complementary therapies work from a paradigm of abundance, where the more an individual gives, the more he or she gains—a critical and essential lesson for life and a practical and spiritual approach for the resolution of the AIDS plague, and, ultimately, for advancing the cause of human justice.

Ana Oliveira is the executive director of Gay Men's Health Crisis (GMHC) and a licensed acupuncturist.