

# SEARCHLIGHT

## NEWS FROM AIDS RESEARCH ALLIANCE

*A National Leader in Fast-Track AIDS Research*

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## In This Issue—

### *Metabolic Disorders Associated With HIV and its Treatment/Part I:*

In this two-part article, Dr. Stephen Brown will review the latest advances in diagnosis and treatment of HAART-related metabolic disorders.

(Article on page 1)

\* \* \*

### *11<sup>th</sup> conference on Retroviruses and Opportunistic Infections*

In this short report Dr. Marjan Hezareh reviews the latest scientific, therapeutic, and clinical data presented at the *11<sup>th</sup> Conference on Retrovirus and Opportunistic Infection (February 8-11, 2004)* held in San Francisco.

(Article on page 6)

\* \* \*

### *Do Diet and Exercise Influence HAART Associated Metabolic Disorders?*

Mr. Noah Manne, exercise specialist, explains the importance of healthy diet in everyone's life, especially in immune compromised patients. He also comments on various training programs beneficial in reducing different metabolic disorders due to the long-term use of HAART.

(Article on page 12)

\* \* \*

### *Prostratin Update*

An outline of the progress that has been made to forward the development of prostratin as an anti-HIV drug targeting the viral reservoirs.

(Article on page 15)

\* \* \*

### *New Clinical Trial*

We are currently enrolling volunteers (HAART-experienced with evidence of excess abdominal fat deposition) for our new trial to reduce abnormal accumulation of fat in HIV-associated lipodystrophy.

(Announcement on page 5)

\* \* \*

### **Metabolic Disorders Associated with HIV and its Treatment Part I: Lipodystrophy, Etiology, Relationship to HAART and HAART Regimen Considerations**

*By Stephen Brown, MD*

Prior to the institution of Highly Active Antiretroviral Therapy (HAART), HIV infection and progression were associated with a host of metabolic abnormalities, including severe wasting, increased incidence of diabetes, fat abnormalities, hypogonadism and changes in lipid profiles.

With the advent of HAART, one would have hoped to see a decrease in these abnormalities presumably due to the reversal of the underlying disease process. Unfortunately, this has not been the case. In addition, further study has also observed additional abnormalities, such as loss of bone density, elevated lactic acid levels, avascular necrosis of hip, knee and shoulder joints and hypertension.

### **Lipodystrophy: A question of definition**

Earlier studies into the causes and incidence of lipodystrophy have been plagued by the lack of common descriptions and definitions. Some studies primarily looked at lipoatrophy, i.e., loss of fat tissue. Others looked at fat accumulation, and some researched combinations of the two. Fortunately the last year has seen significant progress in this area with large studies resulting in both a "HIV Lipodystrophy Case Definition" (LCDC) based on ten factors (Table I) and a correlated clinically developed severity scale. The LCDC score is correlated significantly with the objective "gold standard" measures of lipodystrophy by regional Dual-Energy X-ray Absorptiometry (DEXA) and single slice abdominal CT scans. Sensitivity and specificity are both in the range of 80%.<sup>1</sup> Simpler LCDC definitions are available if all necessary factors are not accessible (e.g. DEXA) but are not as specific or sensitive. (The various scales were developed by the *National Centre in Epidemiology and Clinical Research* in Australia and can be seen at <http://mud.unsm.edu.au/nchecr> or at [http://www.ti3m.com/hiv/default\\_ld.htm](http://www.ti3m.com/hiv/default_ld.htm)).

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# SEARCHLIGHT

NEWS FROM AIDS RESEARCH ALLIANCE

*A National Leader in Fast-Track AIDS Research*

ARA envisions a future in which HIV and its effects are eliminated from infected individuals, and research yields effective and accessible methods to prevent new infections—eradicating the virus.

ARA's mission is to find and accelerate the development of effective treatments for HIV and its complications. We do this by conducting cutting-edge research and clinical trials in order to improve the longevity and quality of life for all people with immune deficiency.

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*The message below was first published two years ago, in response to lagging congressional action on the Early Treatment for HIV Act, legislation that is crucial to the survival of HIV+ Americans. Two years later, Congress has yet to pass the Act and people have died as a result. The bill has just been reintroduced in the House with 70 co-sponsors. The words below are as true today they were when this call for action first appeared. If you read the message, I hope you'll take a moment to communicate your concerns to your congressional representative.*

## Message from the Executive Director

Nearly a million people live with HIV in the United States. Medication to treat HIV/AIDS usually costs between \$10,000 and \$12,000 a year – *over a third of the average income in the United States.* Nevertheless, even the federal government's recent moderation of its earlier, aggressive *Treatment Guidelines* does not change the fact that many still have no access to treatment. Every state also has a federally mandated "AIDS Drug Assistance Program," or "ADAP," to provide treatment access for some. But each state has wide discretion over how access to its ADAP is determined. Some limit the number of people who are eligible. And while New Yorkers on ADAP have access to 471 drugs, Utah and Louisiana offer only 18 to their participants. Federal law allows this disparity, (and California's new governor has just proposed a cap on enrollments for its ADAP.)

You might have reasonably guessed that Medicaid, a federal payer of last resort, covers HIV/AIDS drugs for this group. And it does help some of them. But many are left cold. Take the hypothetical case of a single, 57 year old HIV+ man or woman without children with a total income of \$20,000. That person would be ineligible for ADAP in many states. Shockingly, the same person would also be denied access to Medicaid in any state *unless and until his or her HIV infection progresses so that continued employment becomes impossible, and a doctor "determines" that the unemployment will last at least a year or that the illness will result in death.*

Most HIV+ people qualify for Medicaid only after they progress to a diagnosis of "full blown" AIDS. But HIV+ persons often are advised to begin combination therapy well prior to a diagnosis of AIDS – a diagnosis that could be delayed with early treatment.

AIDS ReSearch Alliance's mission statement mandates that we do research "in order to improve the longevity and quality of life of all people" living with HIV. We all know of the tragedy developing in sub-Saharan Africa, and now in Asia. But how many of us know that many U.S. citizens have no access to drugs, many of which ARA has helped to develop. How ironic that even the official Federal Treatment Guidelines mandate that HIV+ patients who need it should not wait for a diagnosis of AIDS. In short, current federal policy demonstrates the substandard nature of Medicaid's denial of drugs to many who will die sooner than they would have if Medicaid coverage began with medical necessity and not political expedience.

The much ballyhooed dawn of effective HIV medications are cold comfort to those low income Americans from whom Medicaid turns away. *You can help end this situation* by helping to ensure passage of the Early Treatment for HIV Act, or ETHA. This would allow those with HIV to qualify for Medicaid coverage earlier in the course of their infection, helping them to stay well rather than waiting from them to fall ill.

This is only common sense. If you agree, please contact your congressional representatives and urge the passage of the Early Treatment for HIV Act. The Act has now languished in a Senate subcommittee for an entire session.

What are they thinking? That you won't notice. Please do.

Respectfully,

*Irl Barefield*

*Executive Director*

*irl@aidresearch.org*

# NEWS & VIEWS

## Is there a relationship between a decrease in bone marrow density and antiretroviral therapy?<sup>1</sup>

The long-term use of Highly Active Antiretroviral Therapy (HAART) is associated with several metabolic disorders, including lipodystrophy, diabetes, dyslipidemia and alteration in bone marrow density (BMD), and osteopenia.

The pathogenesis of osteopenia in HIV infection is not fully elucidated and the effect of HAART on bone metabolism and on BMD in HIV positive patients is controversial. Some studies demonstrated a relationship between the use of PIs and a decrease in BMD, while others found that BMD remained unaltered after replacing PI-containing regimen. Moreover, a recent study showed that indinavir could have a beneficial effect on BMD over time. On the other hand, osteopenia may involve many other factors such as the direct effect of the virus upon osteogenic cells, persistent activation of cytokines, and alteration in the metabolism of vitamin D and its derivatives.

In order to identify the role of PI-regimens in possible alterations of bone metabolism, Bruera *et al*, in a cross-sectional study, investigated the relationship between BMD and the use of HAART in 142 HIV-positive patients aged 20-45. Patients were divided into four groups: HIV-seropositive antiretroviral naïve patients, HIV-seropositive on antiretrovirals without PIs for over one year, HIV-seropositive on combined antiretrovirals containing PIs, and healthy seronegative subjects. They measured BMD by dual energy X-ray absorptiometry in total body, lumbar spine and proximal femur, and evaluated serum osteocalcin, parathyroid hormone, calcium and phosphates. The results demonstrated that BMD was lower in HIV-positive patients compared to healthy controls, with no significant difference among treatment groups. There was a significantly higher occurrence of osteopenia and osteoporosis in HIV-positive patients compared to healthy subjects, with no differences among treatment-naïve and either of the treatment groups. They suggested that decreases in BMD and occurrence of osteopenia and osteoporosis cannot be attributed to the therapeutic regimen. Furthermore, there was a correlation between years of infection and BMD in all sites studied suggesting the effect of the HIV virus on bone metabolism independent of antiretroviral therapy.

## Second failure for the first experimental AIDS vaccine ([www.vaxgen.com](http://www.vaxgen.com))

In November 2003, VaxGen reported that the experimental AIDS vaccine tested in Thai drug users has failed to prevent transmission of HIV. This study involved 2,547 injecting drug users in Thailand and preliminary results showed that 105 people in a placebo groups became infected with HIV. This is the second time that the vaccine, a

genetically engineered version of HIV surface protein gp120, failed to protect against HIV and has proven ineffective in an efficacy trial. However, NIAID still plans to include the vaccine in a new study involving 16,000 people in Thailand. In this study, the VaxGen vaccine will be used as a booster shot to another AIDS vaccine developed by Aventis Pasteur, which contains canarypox viruses expressing several HIV genes. This decision has been made based on some evidence demonstrating that the combination of the vaccines is more efficient in expansion of CD4 T helper cells, resulting in a more robust immune response against HIV.

## New vaccine against HIV-1 subtype C in South Africa.

The AVX101 consists of the weakened strain of Venezuelan equine encephalitis virus, which acts as a vector carrying HIV-1 genetic material into host cells. This is the first vaccine designed to specifically target the HIV-1 subtype C virus prevalent in South Africa. The aim of the trial is to demonstrate safety and dosage of the vaccine.

## The ability of Dendritic cells to transmit HIV-1 is called into question<sup>2</sup>.

HIV can use the trafficking ability of Dendritic Cells (DCs) to infect permissive CD4<sup>+</sup> T cells. The DC-SIGN expressed by certain DCs (e.g. in genital mucosa) binds the HIV-1 envelope glycoprotein, gp120, and facilitates HIV entry into DCs. These immature DCs migrate to lymph nodes carrying the virus with them, where HIV virus can be transferred to CD4<sup>+</sup> T cells and establish an infection. However, a recent study published in *Blood* showed that virus internalized by DC-SIGN positive DCs is rapidly degraded in an endo-lysosomal compartment. So if HIV is destroyed in DC-SIGN<sup>+</sup> cells, can it enter the antigen-presenting pathway and be recognized by the immune system?

Comparison of wild-type B-cell line with DC-SIGN<sup>+</sup> B-cell line, after exposure to non-infectious HIV, showed that only DC-SIGN<sup>+</sup> cells induce the release of interferon- $\gamma$  by HIV-specific CD8 cells isolated from an infected patient. Using DC-SIGN specific monoclonal antibodies, they showed the importance of DC-SIGN for MHC class-I restriction presentation of virus antigens. They further demonstrated that MHC-I restricted peptides are derived from a small number of virions that enter the cytosol and are degraded by the proteasome, rather than from larger amount of virion degraded in the endo-lysosomal compartment. Since the HIV virus is degraded in DCs, how can DCs transmit HIV to T cells several days after exposure to the virus? Authors suggested that cell contact between DCs and T cells in the lymph nodes might make the transmission so

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# NEWS & VIEWS

efficient that only small amounts of HIV virus avoiding degradation are required to establish infection in T cells. It is also possible that low replication of HIV virus occurs in DCs and transmission of the virus is established through new virions rather than internalized virus.

## Human gene product, Murr1, restricts HIV replication in resting T cells; implication in development of new antiviral drugs<sup>3</sup>.

HIV virus can replicate in quiescent and stimulated CD4 T cells, but not in resting CD4 cells. Restriction factors contributing to the inhibition of viral replication are not yet well identified. In the December issue of *Nature*, Ganesh and colleagues reported that Murr1, a gene product previously involved in copper regulation, inhibits HIV replication in unstimulated CD4+ T cells partly *via* an effect on basal and cytokine-stimulated NF- $\kappa$ B activity. Inhibition of Murr1 gene expression, using specific RNA interference, increases HIV replication in resting CD4 cells. Therefore, Murr1 acts as a genetic restriction factor that inhibits HIV replication. Inhibition of viral replication in resting T cells, as well as in latently infected cells, might affect disease progression and viral rebounds after discontinuation of HAART. In-depth understanding of the molecular mechanism involved in restriction of HIV replication might lead to identification of new genetic factors, such as Murr1, which in turn can help the development of new antiviral drugs delaying progression to AIDS.

## BMS-378806; A small molecule that blocks HIV entry into cells.<sup>4</sup>

Antiretroviral therapy has improved the life expectancy and the quality of life of people living with HIV. However, due to the emergence of drug resistance and toxicity associated with long term use of these drugs, development of new drugs with novel mechanisms of action is needed. One new strategy would be to inhibit infection by blocking HIV binding to its receptor, which subsequently blocks viral fusion and entry into cells. Presently, several molecules inhibiting binding of the virus to its co-receptor are in early clinical trials. BMS-378806 is unique since it is the first molecule that inhibits binding of gp120 to CD4 receptor.

In the September issue of *PNAS*, Lin and colleagues from Bristol-Myers Squibb reported that this small molecule inhibits HIV infection through blocking the binding of envelope glycoprotein, gp120, to CD4 cells. Preclinical testing of BMS-378806 revealed that it exhibits pharmacological activities in extremely low concentrations with minor toxicity and can be administered orally. Since this compound was selected to inhibit subtype B strains of HIV, it

displays weaker activity against HIV strains prevalent in Africa and Asia and has no effect on HIV-2 and SIV. Analysis of HIV resistant mutants generated in the presence of BMS-378806, revealed that some of the mutations lie outside the CD4 binding pocket and also mutations were found in the gp41 region suggesting that BMS does not fit exactly in CD4 binding pockets. Therefore, the structure of BMS-378806 might be considered as a first generation molecule that would lead to more efficient and improved HIV binding inhibitors. New compounds that fit more snugly into CD4 binding pockets might exhibit higher potency and be active against a wider variety of HIV strains.

## How HIV uses protein from human cells to overcome recognition by restriction factor and innate immunity.<sup>5</sup>

Many human and non-human primates express cellular inhibitors or restriction factors that confer host resistance to retrovirus infection. In humans, the restriction factor is called Ref-1, but unfortunately, HIV-1 is able to neutralize this defense. Towers and colleagues investigated the mechanism of this neutralization and demonstrated that HIV-1 recruits host protein cyclophilin A (CypA) into a complex with the virion capsid protein, thereby inhibiting recognition of infectious virus by Ref-1. In contrast, in some monkeys' formation of this complex (HIV Capsid:CypA) renders virions highly sensitive to simian restriction factor Lv-1. This observation correlates with the inability of HIV-1 to infect any monkey species. They showed that the HIV-1 capsid protein binds to the CypA and camouflages the target site for human Ref-1. In contrast, binding of HIV capsid protein to CypA creates a target for monkey LV-1 restriction factor. Further investigation into the mechanism of action of Ref-1 in humans and Lv-1 in monkeys will help us find a way to reinforce the ability of Ref-1 to control HIV-1 infection and also help in development of more suitable animal models to study HIV pathogenesis.

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# A New Study to Reduce Abnormal Accumulation of Fat in HIV-Associated Lipodystrophy.

Serono<sup>®</sup>, Inc.

## Title

A phase III, multicenter, randomized, double-blind, placebo-controlled, parallel group study of the safety and efficacy of Serotism<sup>®</sup>, in the treatment and maintenance of Human Immunodeficiency Virus-associated Adipose Redistribution Syndrome (HARS).

## Background

Highly active antiretroviral therapy (HAART) has decreased viral load to undetectable levels and improved the quality of life of HIV-infected patients. However, long-term use of HAART is associated with several toxicities such as abnormalities of fat redistribution and metabolism called HIV-lipodystrophy syndrome. The fat distribution abnormalities include abnormal fat depletion, abnormal fat accumulation only, or both abnormal fat depletion and accumulation. HIV-associated Adipose Redistribution Syndrome or HARS is a subset of HIV lipodystrophy. The defining characteristic of HARS is abnormal accumulation of truncal fat, including visceral adipose tissue (VAT) in an HIV-infected patient. Some patients may also present increased dorsovisceral fat called buffalo bump. No therapy is currently approved to treat abnormal fat redistribution. A previous trial suggested that Serotism<sup>®</sup>, can significantly reduce truncal fat, non-HDL cholesterol and related cardiovascular risk parameters in HIV-infected patients. This placebo-controlled trial is designed to confirm these findings.

## Study Design

The purpose of this trial is to confirm the 12-week findings of the effect of Serotism<sup>®</sup>, (4 mg daily versus placebo at 12 weeks) on visceral adipose tissue (VAT). This trial will also investigate the effect of 2 mg alternate day Serotism<sup>®</sup>, or placebo on VAT as a maintenance therapy during weeks 12-36.

**Period I (12 weeks):** *Volunteers are randomized to the following groups:*

- **Group A:** Serotism<sup>®</sup>, 4 mg/day
- **Group B:** Placebo

## Period II (Week 12-Week 36)

- **Group A:** Volunteers will be re-randomized to a 1:1 ratio receiving either:
  - Group A1:** placebo administered on alternate day
  - Group A2:** Serotism<sup>®</sup>, 2 mg administered on alternate days
- **Group B:** Volunteers will receive placebo on alternate days until week 24. Then open-labeled therapy with Serotism<sup>®</sup>, 4mg/day will be administered for 12 weeks (week 24-week 36).

## Primary Objective & Endpoints

The primary endpoint of this study is to determine if Serotism<sup>®</sup>, administered for 12 weeks reduces VAT assessed by computerized tomography or CT scan compare to placebo. Secondary endpoints include changes in VAT and subcutaneous adipose tissue (measured by CT scan), changes in trunk fat and other body composition parameters (assessed by Dual Energy X-Ray Absorptiometry, DXA) such as limb fat, trunk: limb fat ratio, total body fat and lean body mass

## Dosing

HIV-positive volunteers, who meet the inclusion criteria, will be randomly assigned to groups.

## Inclusion Criteria (*partial list*)

1. Documentation of HIV infection
2. Have evidence of excess abdominal adipose deposition
3. ≥ 18 years old
4. Taking antiretroviral medications for 30 days prior to study entry

## Number of Volunteer Slots estimated at ARA

6-20

## Principal Investigator

Stephen J. Brown, M.D.

# 11th conference on Retroviruses and Opportunistic Infection: Conference Briefs

By Marjan Hezareh, Ph.D.

## What are we waiting for?

The World Health Organisation (WHO), in conjunction with UNAIDS, designed the recent “3 By 5” initiative to provide treatment to three million HIV positive patients by year 2005, which would have a significant impact on the worldwide HIV/AIDS pandemic. The initiative is based on the recognition that prevention is strengthened if treatment is available.

It is well recognized that a major barrier to delivering ARV (antiretrovirals) in African countries, for example, is that less than 2% of the population is tested for HIV. In his keynote lecture at the conference, Ambassador Stephen Lewis, United Nations special envoy on HIV/AIDS in Africa, pointed out that “a prognosis of death, without hope, is hardly an inducement to seek the prognosis.” It is clear that access to treatment through well-designed protocols would increase the likelihood of people seeking HIV/AIDS testing.

To be effective, the “3 By 5” initiative cannot “end” in 2005, since ARV does not cure HIV infection and lifelong treatment should optimally be continued for everyone who has begun treatment. The reduction of anti-HIV drug costs, design of simpler drug regimens, increased funding, and the improvement of political climates will be important factors towards influencing the success of the “3 By 5” initiative.

The WHO has already pre-qualified a triple fixed-dose combination drug (one pill twice a day) available from a generic manufacturer at a very low price of \$132 per person per year. In addition, the WHO will need to train thousands of people, hire teams of experts and implement service infrastructures in each country. For “3 By 5” to be a success, the WHO needs at least \$200 million over its existing budget and they will need it in 2004.

A potential source of support revenue could be the individual contribution of prosperous countries, but so far no such nation has donated an adequate sum of money to either the WHO or the *Global Fund for AIDS, Tuberculosis and Malaria*. The “3 By 5” initiative has raised great hopes and expectations—it would be tragic if it were to fail because of lack of funding.

It is to be hoped that worldwide governments will look at the example of Africa and realize that delay spells disaster in the AIDS epidemic. It is estimated that there are 4.1 million HIV-infected Africans requiring treatment, but only approximately 700,000 are actually receiving ARV. In some countries half the population succumbs to AIDS and all of Africa’s famines are now AIDS-related: hungry people lack the strength to fight off sickness, sick people lack the strength to grow food, and dead parents cannot teach their children how to farm.

Even if “3 By 5” reaches its target of treating three million people worldwide, another three million are in desperate need of treatment by end of 2005. “There is no limit to the will and resources available to fight terrorism; what happened to the will and the money to fight the war against AIDS?” questioned Ambassador Lewis, “We have over twenty million dead—what in heaven’s sakes we are waiting for?”

## Women and HIV

Continuous focus on prevention is critical to expand ARV availability. Challenges in extending treatment to women of child-bearing age may be compounded by emerging data on the high prevalence of resistance associated with single-dose nevirapine used to prevent HIV transmission from mother to infant. According to UNAIDS an emerging group of people who are increasingly at high risk

of contracting HIV are married women in Africa.

The once prevailing assumption that commercial sex is the primary way that women get infected no longer holds. In marriage the power imbalance is too great to permit or to request the regular use of condom. The ABC prevention model (abstinence, be faithful, or use condoms) used in Uganda has worked because it has given people a menu of choices.

But as Ambassador Lewis said in his keynote remarks, the ABC model does not work “in the one place where the risk for the women may be the greatest”. Two thirds of the 10 million Africans between the ages of 15 and 24 years are girls and women. The only strategy that allows women to protect themselves without partner consent is the use of microbicides. A wide range of products, including detergents, charged compounds, acidic compounds, antibodies, antivirals, and probiotics are in development. However, none of these compounds fulfills all of the criteria desired. In addition, it is estimated that the first such product might not be available before 2010. While funding for microbicide development has improved and enthusiasm is high, development of a successful product will require overcoming a variety of major biological barriers and the completion of very large, expensive clinical trials.

## Mother-to-Child Transmission

According to WHO, in 2003 alone 2.5 million children were infected with HIV, mostly through mother-to-child transmissions. Worldwide in 2004, over 500,000 children died of AIDS. Researchers demonstrated in a Thailand-based study that administering a single dose of nevirapine to mother and infant, in addition to an AZT regimen, could reduce the risk

of mother-to-child HIV transmission to below 2%, a result similar to those achieved using ARV during pregnancy. In the absence of any medical intervention, the rate of transmission can be as high as 35%.

### AIDS in the USA

The *Center for Disease Control (CDC)* has released new data on HIV prevention, treatment and risk behaviors in the US.

- Despite the public health goal of providing *Pneumocystis Carinii Pneumonia (PCP)* prophylactic to 95% of HIV-infected Americans by 2010, new data demonstrated that 20%, or one in five, of those eligible for PCP prophylaxis (usually Bactrim™) do not receive it. Researchers emphasized that increase vigilance about PCP prophylaxis is critical, especially among patients with CD4 counts below 200.
- It is well known that syphilis can facilitate the acquisition and transmission of HIV infection. Despite a 1,000 % increase in syphilis rates from 1998-2002 among men who have sex with men (MSM) in San Francisco, a new study found no apparent increase in HIV incidence among MSM in two HIV-testing populations. However, authors cautioned that the study was limited to men receiving HIV testing at testing sites and may not be representative of all MSM in San Francisco. They hypothesized that sero-sorting, whereby MSM choose partners of the same sero-status (i.e., HIV+ or HIV-) could account for the lack of associated HIV transmission with syphilis infection rates. They also called for integrated HIV and STD prevention programs for San Francisco MSM to help stop the spread of syphilis and prevent increases in HIV infection.
- A study investigating HIV transmission in black MSM college students and non-college students in North Carolina showed that high-risk sexual behaviors were common among HIV-infected and uninfected both

in college and in the community and that HIV/STD prevention programs targeting young black MSM are urgently needed.

- CDC behavioral scientist Dr. Greg Millett defines the term “men on the down low” as heterosexually-identified, bisexually active black men who do not disclose their same-sex behavior to their female partners. He pointed out that limited scientific research has been done to help understand the risk of HIV infection among men on the “down low” and their partners. Most data on black MSM are drawn from samples of primarily gay or bisexually-identified black men and may not be applicable to men on the “down low”—more research is needed to determine where they belong in the spectrum of HIV risk in black males.

### Antiretroviral therapy and emergence of drug-resistant mutations

In an effort to increase patient adherence and compliance, much attention has focused on simplifying ARV regimens. However, a series of reports suggested that some regimen simplification could result in rapid treatment failure accompanied by the emergence of drug-resistant mutations. Of particular concern is the emergence of the 65R reverse transcriptase mutation related to the omission of AZT from antiretroviral treatment regimens. Specifically, certain antiretroviral combinations containing tenofovir, lamivudine (3TC), didanosine or abacavir cannot fully suppress viral replication in the presence of the reverse transcriptase mutations 65R and 184V.

To investigate the trends in the prevalence of 65R, Dr. Mellors and colleagues searched databases for the frequency of 65R and its association with other nucleoside reverse transcriptase inhibitor (NRTI) mutations. Out of 60,000 samples that contained any NRTI mutations, they found that 65R frequency increased from 0.8% in 1998 to 3.8% during 2003. In addition, they found that 65R is a multi-NRTI resistance mutation that

reduces susceptibility to all D-, L-, and acyclic NRTIs, tested except those containing a 3'-azido moiety. The increased prevalence of the previously rare 65R mutation appears to be due to the use of nucleoside combinations that lack AZT.

Another study (Dr. R. Elion of the George Washington School of Medicine in Washington, DC) demonstrated poor virologic response and rapid emergence of drug resistance among 88 antiretroviral naive patients receiving once-daily combinations of trizivir (AZT, 3TC, abacavir) and tenofovir. Once-daily treatment with a triple nucleoside regimen containing didanosine, 3TC and tenofovir also led to a high frequency of poor virologic response and the early emergence of drug resistance.

An important implication in the treatment of antiretroviral-naïve patient and transmission of resistant virus came from a study of twelve patients with primary HIV infection who had deferred antiretroviral therapy (Dr. Susan J. Little, University of California, San Diego). Most patients had only limited reversion to wild type, retaining resistant variants in plasma HIV RNA. This study demonstrated that drug-resistant HIV variants might persist in untreated individuals with primary HIV infection for more than 3 years. Nine out of ten patients with NNRTI mutations had greater than 10-fold reduced susceptibility to all three NNRTI drugs. None of the four patients with resistant mutations to PI drugs exhibited any reversion to susceptible wild type virus during the study period. The authors proposed that the relatively high replication values of the transmitted resistant variants also suggest that selective pressures at transmission may in fact favor the transmission of those resistant variants.



## CURRENT RESEARCH AT ARA

STUDY	DESCRIPTION	STATUS
<p><b>Pre-Clinical &amp; Basic Research</b> AIDS RESEARCH ALLIANCE</p>	<p>AIDS ReSearch Alliance is engaged in a number of ongoing preclinical and basic research projects necessary prior to human clinical trials. For example, see the <i>prostratin update</i> on page 15 outlining important progress that has been made to advance the development of prostratin as an anti-HIV drug.</p>	<p>Ongoing</p>
<p><b>Serostim® 24380</b> SERONO</p>	<p>A phase III, multi-center, randomized, double-blind placebo-controlled, parallel group study of the safety and efficacy of Serostim® (mammalian cell-derived recombinant human growth hormone, r-hGH) in the treatment and maintenance of Human Immunodeficiency Virus-associated Adipose Redistribution Syndrome (HARS).</p>	<p>Enrollment &amp; study pending</p>
<p><b>C107</b> NEUROGESX</p>	<p>A randomized, double-blind, controlled dose-finding study of NGX-4010 (capsaicin) for the treatment of painful HIV-associated distal symmetrical polyneuropathy.</p>	<p>Enrollment ongoing; study ongoing</p>
<p><b>AG4301010</b> AGOURON/PFIZER</p>	<p>An open-label study of the pharmacokinetics, safety and efficacy of optimized Viracept™ therapy as a component of HAART in treatment-naïve subjects.</p>	<p>Enrollment ongoing; study ongoing</p>
<p><b>Experimental HIV Vaccine</b> MERCK &amp; CO., INC.</p>	<p>A phase I dose-ranging study of the safety, tolerability, and immunogenicity of the Merck trivalent adenovirus serotype 5 HIV-1 gag/pol/nef vaccine in a prime-boost regimen in healthy adults.</p>	<p>Enrollment ongoing; study ongoing</p>
<p><b>BMS AI266-406</b> BRISTOL-MYERS SQUIBB</p>	<p>Vest-QD: a phase IV, open-label, randomized, multicenter study switching HIV-1 infected subjects with a viral load &lt;50 copies/ml on a first PI-based regimen to an efavirenz substitution regimen.</p>	<p>Enrollment ongoing; study ongoing</p>
<p><b>BMS AI424-067</b> BRISTOL-MYERS SQUIBB</p>	<p>A phase IIIB, open-label, randomized, multicenter study evaluating the effect on serum lipids following a switch to the protease inhibitor (PI) atazanavir in HIV-1 infected subjects evidencing virologic suppression on their first PI-based antiretroviral therapy.</p>	<p>Enrollment ongoing; study ongoing</p>

STUDY	DESCRIPTION	STATUS
<p><b>C0603</b> SAVIENT PHARMACEUTICALS, INC. AND THE NEURO-AIDS RESEARCH CONSORTIUM (NARC)</p>	<p>A randomized, double-blind, placebo-controlled, multicenter, dose-ranging study to evaluate the efficacy and safety of prosaptide over 6 weeks of treatment for the relief of neuropathic pain associated with HIV-1.</p>	<p>Enrollment ongoing; study ongoing</p>
<p><b>Capravirine A4311002</b> PFIZER/AGOURON PHARMACEUTICALS, INC.</p>	<p>A double-blind, randomized, placebo-controlled study of capravirine (AG1549) in combination with Viracept™ and two nucleoside reverse transcriptase inhibitors in HIV-infected patients who failed an initial nonnucleoside reverse transcriptase inhibitor containing regimen.</p>	<p>Enrollment complete; study ongoing</p>
<p><b>Capravirine A4311006</b> PFIZER/AGOURON PHARMACEUTICALS, INC.</p>	<p>A phase II, randomized, double-blind, dose-ranging study of capravirine (AG1549) in combination with Kaletra™ and least 2 nucleoside reverse transcriptase inhibitors in HIV-infected subjects who have failed antiretroviral regimens containing protease inhibitors, nonnucleoside reverse transcriptase inhibitors, and nucleoside reverse transcriptase inhibitors.</p>	<p>Enrollment complete; study ongoing</p>
<p><b>Zerit® (Stavudine)</b> BRISTOL-MYERS SQUIBB</p>	<p>Evaluation of the safety and antiviral activity of stavudine extended release formulation as compared to stavudine immediate release formulation, each as part of potent antiretroviral combination therapy.</p>	<p>Enrollment complete; study ongoing</p>
<p><b>Micronutrient Neuropathy Study</b> INTEGRATIVE HEALTH CONSULTING, INC.</p>	<p>Broad-spectrum micronutrient supplementation in HIV-infected patients who develop peripheral neuropathy while taking stavudine and/or didanosine antiviral therapy.</p>	<p>Study complete; report pending</p>
<p><b>Serostim™</b> SERONO LABORATORIES</p>	<p>A study testing the safety and effectiveness of a growth hormone in treating HIV-associated lipodystrophy.</p>	<p>Study complete; report pending</p>
<p><b>BioMerieux 226034</b> BIOMERIEUX, INC.</p>	<p>Clinical evaluation of Vironostika HIV-1 Plus O Microelisa System on serum/plasma and dried blood spots enrolling HIV-negative volunteers.</p>	<p>Study completed; report pending</p>

*For information about enrolling in any of our studies, contact Corie Castro at 310.358.2429. Assistance with transportation to our clinical research facility is usually available upon request. For priority notification of new clinical trials, sign-up for our Priority Notification Program when you call.*

## Metabolic Disorders Associated with HIV and its Treatment: Part I

*continued from page 1*

In a further development, the LCDC has been correlated with patient and physician assessments of lipodystrophy in eight body areas using a different scoring system, the HIV Outpatient Study scale (HOPS).<sup>2</sup> In this scale, the eight regions are rated for the presence of fat abnormalities (either an increase or decrease) on a scale of 0-3 corresponding to absent (0), mild (1), moderate (2) or severe (3). The rating is based both on abnormal fat loss as well as on accumulations of fat. Correlations with the LCDC are in the 0.6 range, which is not perfect but nonetheless demonstrates a significant advance in the field. While the development of such definitions may seem overly academic or arcane, it is critical work necessary to better assess the incidence and prevalence of lipodystrophy. Furthermore, they are crucial in determination of intervention and measurement of their impact on treatment.

### Cause(s) of lipodystrophy, insulin resistance and other metabolic disturbances

Avoidance or treatment of metabolic abnormalities is best directed when the underlying etiologies are understood. Unfortunately there is conflicting information about the relative contribution of factors, be it disease, treatment or host factors.

*In vitro* (test-tube) experiments looking at the effects of various classes of antiretroviral medications on mitochondrial DNA, adipocytes, and other cells have pointed to a number of potential contributing factors that may play a role in the development of these abnormalities.

Among these are the findings that the approved Protease Inhibitors (PIs) can inhibit glucose and lipid uptake into fat cells and increase lipolysis (fat breakdown) by fat cells. Additional effects on GLUT4 (a major glu-

cose transporter mechanism in the uptake of glucose into cells) translocation to the cell membrane and downstream effects included impaired signaling via PDK1. This would theoretically result in insulin resistance and decreased glucose movement from blood into adipocytes. Additional protease effects include frank adipocyte toxicity that may reduce the number of fat cells in various compartments to varying degrees. Additional effects on sterol regulatory element binding protein-1 (SREBP-1c) intranuclear localization results in inhibition of pre-adipocytes differentiating into mature fat cells. Other experiments show dysfunction of many other cellular factors, too numerous to recount here.

Nucleoside Reverse Transcriptase Inhibitors (NRTI's) have also been examined for their deleterious effects on several cell types and cellular functions. In experiments on cultured adipocytes, the NRTIs, d4T and ZDV decreased cell lipid content and mildly increased cell death (apoptosis), while abacavir, 3TC and ddI had no effect. An increase in insulin resistance in the presence of ZDV was also observed.<sup>3</sup> Studies of the NRTIs in enzyme assays and cell cultures demonstrated inhibition of DNA polymerase gamma and other mitochondrial enzymes, which can gradually lead to mitochondrial dysfunction and cellular toxicity. The NRTIs, ddC, ddI, and d4T have greater toxicity than 3TC, ZDV and Abacavir. Other *in vitro* experiments have documented impairment of additional mitochondrial enzymes such as adenylate kinase and adenosine diphosphate/adeno-

**Table 1. Diagnosis of HIV-Associated Lipodystrophy, Case Definition-Complete Data list (National Centre in HIV Epidemiology and Clinical Research).**

Gender
Age
HIV Duration
CDC Category
Waist-Hip Ratio
HDL-Cholesterol
Anion Gap
VAT:SAT Ratio (Intra <i>vs</i> Extra Abdominal fat ratio, by CT scan)
Trunk:Limb Fat Ratio (by DEXA)
Leg fat % (by DEXA)

sine triphosphate translocators. The clinical manifestations of NRTI-induced mitochondrial toxicity include hepatic steatosis, lactic acidosis, myopathy, nephrotoxicity, peripheral neuropathy and pancreatitis.<sup>4</sup> There is evidence showing that the impairment seen in *in vitro* assays using cultured cell lines is even more evident and pronounced in patient-derived adipocytes, especially with respect to d4T and stavudine.<sup>5</sup>

Effects of the Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)<sup>6</sup> efavirenz on pre-adipocytes and adipocytes differentiation and metabolism have also been studied. In the presence of efavirenz, primary human pre-adipocytes failed to accumulate cytoplasmic triacylglycerol droplets, while in already matured adipocytes, a moderate but reversible decrease in cells' triglyceride content was observed. The effects of efavirenz on adipocytes' metabolism was primarily due to a decrease in gene and protein expression of the lipogenic transcription factor sterol regulatory binding-element protein-1c (SREBP-1c). They also demonstrated that basal metabolism of glucose, lipolysis and apoptotic pathways were not involved. Taken together, these results demonstrated that efavirenz induced strong inhibition of the SREBP-1c pathway contributing to adipose tissue atrophy.

### Effects of HIV infection and HAART therapy on lipoatrophy and lipodystrophy in HIV positive patients

Early associations between different HAART regimens have suggested that different combinations of HAART regimens are associated with either lipoatrophy, or fat accumulation in HIV positive patients. In particular, several studies showed

that the administration of d4T with or without ddI was associated with lipoatrophy. Some cross-sectional studies suggest that the addition of older PI's to these regimens may accelerate these lipodystrophic changes. Yet several studies have pointed to factors unrelated to HAART regimen and showed that the multifactorial contributions to morphological changes such as initiation of therapy at older age, lower Body Mass Index (thinner individuals), individuals with more advanced disease, and longer duration of HAART are implicated in development of both lipoatrophy and lipodystrophy and cannot be undermined. Furthermore, measurement of chemokines and other biological markers such as leptin (lower in lipodystrophy), tumor necrosis factor (TNF) receptor plasma levels (higher in lipodystrophy), TNF alpha secretion from abdominal SAT (higher with lipodystrophy), Il-6 (higher in lipodystrophy) and hyperandrogenemia showed that women are more likely to develop fat accumulation than men and are predisposed to lipodystrophy.

While the combination of varying HAART regimens can be associated with morphologic changes, causality can only be assessed by conducting prospective studies. There are multiple ongoing and continuing studies attempting to assess prospectively the effect of different HAART regimens on lipodystrophy. The studies fall generally into two broad categories: switch studies and comparison studies. In switch studies, patients on a particular regimen (associated with lipodystrophy) are either kept on the same regimen or changed to a potentially less lipodystrophic regimen (generally away from a PI containing regimen) to see if there can be reversal or at least non-progres-

sion of lipodystrophic morphological changes. In the comparison studies, antiretroviral naive volunteers are begun on two different regimens, one purportedly better suited to avoid lipodystrophy. These patients are then followed head to head looking for the development and progression of lipodystrophy. There is preliminary data from these studies suggesting that some regimens are better for preventing lipodystrophy than others. But it is not determined whether the primary goal of viral suppression, i.e., preventing progression to AIDS will be served by all combinations. Recently a study of three antivirals (AZT, 3TC, ABC) was terminated when it was determined that this combination is not efficient in maintaining suppression while it was expected that this combination would have a favorable profile with respect to the development of lipodystrophy.<sup>7</sup>

One caveat about these studies is that the development and also the reversal of lipodystrophic morphological changes may take considerable time. Some studies have seen few or no differences for the first year in both groups, and differences have only emerged when the studies have been ongoing for several years. Similarly, switch studies have indicated that reversal of lipodystrophy may be measurable but is very subtle (un-noticed by patients) and that redistribution or reconstitution of adipose tissue may take up to 3 years or more. Therefore, comparison of results from shorter *vs.* longer term studies is hazardous at best. At this point, the relative long term antiviral effectiveness (maintenance of viral suppression) of the varying regimens may play a role as well since it is obviously important that patients remain suppressed.

*continued on page 14*

## Do Diet and Exercise Influence HAART-Associated Metabolic Disorders?

By Noah Manne

Diet and exercise are important in anyone's life, whether a compromised immune system is an issue or not. The body was made to be used, and lack of use will make it function less than optimally. "If you don't use it, you lose it." couldn't be truer. Doing almost anything physically active is better than doing nothing, but being informed about what to do and what *not* to do can make a big difference in the amount and quality of change you are able to effect in your wellbeing. Learning how to keep yourself as fit as possible can provide real advantages and benefits, both physical and psychological, for managing your HIV condition.

Make no mistake—poor eating habits and physical inactivity can decondition even a healthy body, and will most likely weaken a compromised system. Conversely, exercise and proper diet will strengthen any system. It goes without saying that it is important to nurture and strengthen a body compromised by any virus. In the HIV + community, it has been found that it is not only the virus that can be debilitating, but the various meds administered to cope with the virus have proven to have side

effects than can make an HIV+ situation even more challenging. These various meds can cause insulin resistance, hypertension, osteopenia, heart disease, and lipodystrophy. The effects of all of these conditions can be mitigated by exercise and proper diet, but exercise can influence each one differently and should be applied in an informed way.

Everyone, whether positive or negative, ought to take a close look at their diet. Most of us have poor eating habits, even those of us who think we eat in a fairly healthy way. We should all be eating low glycemic index foods. High glycemic index foods shoot the insulin level up fast and make it come crashing down just as dramatically, causing a craving for more of the same kinds of foods to lift the insulin level up again and take us out of the "sugar blues" we feel after the crash. A long-term rollercoaster blood sugar ride can lead to excess body fat and insulin conditions such as adult-onset diabetes. Low glycemic index foods affect a gradual rise in the insulin level, causing lower highs and higher lows, keeping insulin levels on a more even keel. High glycemic index foods are high in sugar and starchy carbs. You can be sure

that most foods found in plastic wrappers and cardboard boxes have a high glycemic index. The less processed the food, the better.

The body best assimilates foods in their original state. Meat, fish, poultry, vegetables, fruit (not dried fruit!) and nuts. If you pick a wheat stalk right out of the ground and eat it, you'll be fine. It is when you eat that wheat stalk after it's been processed a number of times until it is finally used as an ingredient in your cereal (no one should ever eat boxed cereal!) or your sandwich bread that you will find your insulin level shooting up. The government invested a lot of money and education in the high carb/low fat concept, and it has taken them a long time to backpedal after making that investment, yet we have more obesity and diabetes in our country than ever before. The low-carb theory continues to gain a stronger foothold in conventional nutritional thinking. Low-carb does not mean no carbohydrates; it relates more particularly to the kinds of carbohydrates one eats. A combination of protein, carbohydrates and fat should be a part of every meal. Low glycemic index carbohydrates can be found in certain fruits

and vegetables. Pasta is refined and has high glycemic index. So are rice and bread. Let's be realistic: pasta, rice and bread are commonly eaten. While they are not things we should be eating, they are things we *will* be eating. Accepting that, we can adjust the quantity of those foods that we eat. We get into trouble when high-glycemic index foods become the staple of our diet. Have pasta once a week instead of every day. Have a tuna salad most days and a tuna sandwich once in a while. Dietary changes alone can have a dramatic effect on the body's functioning and appearance.

Exercise can also positively affect an insulin resistance condition. Whenever you build lean muscle mass, you increase your metabolism and burn body fat. Excess body fat causes problems with the absorption of glucose in the blood system, which is what is behind the various insulin resistance conditions. Weight resistance training is not the only means of gaining lean muscle mass, but it is probably the most effective way. One benchmark by which to measure gains in lean muscle mass is the following: If you are able to do more this week than you did last week, you are getting stronger. If you are getting stronger, you are building muscle mass. If you can bench-press ten pounds more than you did last week, you can do so because you have more muscle to do it. If you can climb up

the canyon this week in the same amount of time as you did last week but with a loaded knapsack on your back, you are stronger and, therefore, more "muscular." The point is that you can gain muscle inside or outside of a gym. You can gain muscle swimming, hiking, doing calisthenics at home, and lifting weights in a gym. If you don't like one way of being physically active, you can find another way. And you—*everyone*—ought to be physically active to build and maintain lean muscle mass and decrease excess body fat.

There is no better exercise for osteopenia, or any condition involving bone loss, than weight resistance work. When older people suffer from osteoporosis, the common prescription is weight resistance exercise to increase bone density. Cardiovascular conditioning is good for overall health; anyone can profit from improving the flow of blood to and from the heart. For increased bone density, however, there is no substitute for weight resistance training.

If you suffer from any kind of heart disease or hypertension, it is always wise to consult your physician before embarking upon cardiovascular conditioning. You will most likely be advised to start with a low to moderate level of intensity. As your condition improves, you will always strive to increase your cardiovascular capacity. Conservative increases in

intensity are still increases. Rushing your rate of increase, however, can be perilous. Slow gains are always the most long-lasting gains.

Cardiovascular conditioning is important in maintaining a healthy ratio of lean muscle mass and body fat. If you manifest signs of lipodystrophy, cardiovascular training can be very helpful in effecting a change. However, depending on the type of wasting, the level of intensity of training is important. If you show signs of wasting, a moderate level of cardio exercise is recommended. However, if you have evidence of fat reappportionment (e.g., abdominal fat), longer cardio workouts with increased heart rate will be effective in burning fat. In either case, however, resistance training to increase lean muscle mass is very important.

No matter where you are with your HIV status, it is vitally important to keep your body in the best shape possible, either as insurance for the future or as a means to forestall a deteriorating condition. Informed and consistent work will give you the best results. Make exercise and good eating habits the framework of your lifestyle so that they become as basic to your day-to-day living as brushing your teeth.

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*Noah Manne is a nationally-recognized clinical exercise specialist and personal fitness trainer who specializes in medical and rehab conditions. Contact him at NManne@aol.com.*


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## Metabolic Disorders Associated with HIV and its Treatment: Part I

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### Current treatment modalities and approaches

Since many prior studies have used varied case definitions, study designs, and study follow-up lengths, direct comparison between HAART regimens is difficult. Hopefully, wide adoption of the LCDC and the Lipodystrophy Severity Scale should make comparisons easier.

Given difficulties comparing studies, it is not surprising that recent USDHS guidelines on the treatment of HIV in adults and adolescents are reticent to make specific HAART recommendations based purely on lipodystrophy considerations. Fortunately the *British HIV Association* has provided some broad guidance in this area.<sup>8</sup> In their recently released new recommendations, they point out that lipoatrophy is difficult to treat and therefore best avoided in the first place. Towards this end they recommend avoiding d4T in an initial regimen.

They recommend not only the treatment of insulin resistance (more on this in the next issue) but also abnormal lipid profiles should be treated by switching regimens where possible and also by the use of lipid lowering drugs. Exercise and diet are recommended but expected to have only modest effects on lipid abnormalities and lipodystrophy.

*The next issue of Searchlight will examine in more detail other modalities of treating lipodystrophy, and treatment of glucose and lipid abnormalities with insulin-sensitizing, lipid lowering and other drugs and hormones. In addition, other metabolic abnormalities including lactic acidosis, bone metabolism changes, and liver toxicity will be discussed.*

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## PROSTRATIN UPDATE

The *phorbol ester* prostratin, used in Western Samoa as an ethnobotanical treatment for viral hepatitis, was isolated at NCI in 1992. Prostratin up-regulates expression of viral products from latently infected cells such as U1 and ACH-2 cell lines. It also inhibits the replication of HIV-1 and prevents viral spread. Prostratin represents a distinct subclass of Protein Kinase C (PKC) activators, based on the fact that it is non-tumor promoting. The lack of tumor promotion of prostratin, coupled with its ability to up-regulate latent HIV-1 provirus expression, are important features that could be exploited as an effective therapy to target latent reservoirs for patients on Highly Activate Antiretroviral Therapy (HAART). In March 2001, AIDS ReSearch Alliance in-licensed prostratin from the National Institute of Health (NIH) and is aggressively moving prostratin through the drug development pipeline. Considering the critical issue of latent virus in HIV chemotherapy, it is vital to enter prostratin into clinical trials as soon as possible.

The following progress has been made since the last issue of *Searchlight* to advance the development of prostratin as an adjunctive therapy targeting the elimination of the HIV reservoir:

- A paper from Dr. Eric Declerc (Rega Institute, Belgium) laboratory was published in the journal *Antiviral Chemistry & Chemotherapy* (Witvrouw et al., "Potent and selective inhibition of HIV and SIV by prostratin interacting with viral entry." *Antiviral Chemistry & Chemotherapy*, 14:321-328, 2004). They demonstrated that prostratin exhibits a potent anti-viral activity against various strains of HIV and that prostratin inhibits the entry/fusion step in the replication cycle of HIV by interacting with a cellular target necessary for viral entry.
- Dr. Michelangelo Foti (University of Geneva, Switzerland) demonstrated that prostratin, similarly to PMA, rapidly reduces cell surface expression of CD4 and CXCR4, but not CCR5, by inducing their endocytosis (internalization of the receptor). Internalization of CD4 and CXCR4 is mediated by the activation of conventional and novel Protein Kinase C (PKC) in response to prostratin or PMA. A manuscript is submitted to *Journal of Immunology*.
- A grant application was submitted to NIH Inter-Institute program Committee for the development of AIDS-related Therapeutics (DART-IIP) proposing further toxicology studies for prostratin. This grant is entitled: In Vivo Toxicology of Prostratin in Rats and Dogs and Distribution of Prostratin Using Radio-Labeled Drug.



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# If your boat is sinking, you've got three options:

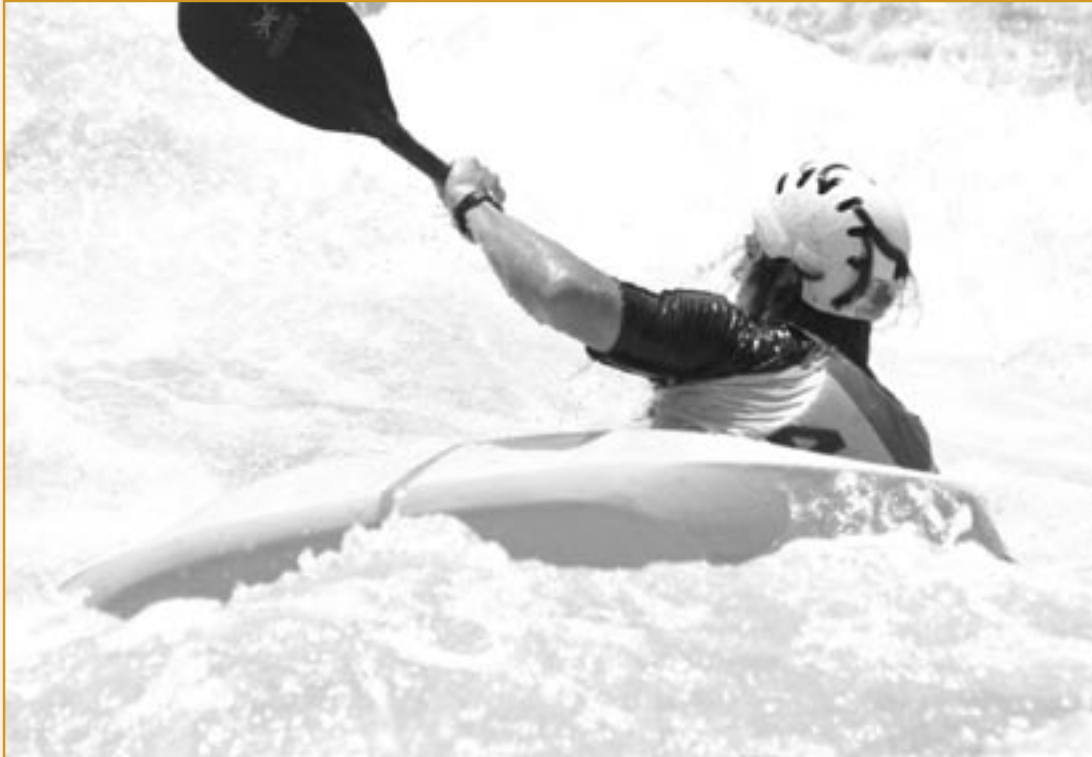


Photo by Leah-Anne Thompson/istockphotos.com

## drown, bail water or start paddling.

Globally, AIDS is a boat sinking at the rate of 8,000 deaths and 14,000 new HIV infections each day. Bailing water out of a sinking boat is a temporary fix, but we really need to get that boat out of the water and safely to shore.

Research does this by looking for long-term solutions to the crisis. Like stronger, more affordable therapies, methods to strengthen damaged

immune systems, and ways to prevent further spread of HIV.

AIDS ReSearch Alliance works to provide answers to this epidemic. When you help fund this life-saving medical research, you are grabbing ahold of an oar and helping us move closer to shore. Please support this work and our effort to find lasting solutions to the AIDS crisis.

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