



UCSD | Antiviral Research Center

# Updates

QUARTERLY Volume 1 issue 1  
Fall 2001

Dear Readers,

Welcome to the AVRC Updates – our new newsletter. As of July 1, 2001 we have officially changed the name of our research center from the Treatment Center to the Antiviral Research Center (AVRC). With this name change, we are both renewing our commitment to excellence in HIV research and broadening our research agenda to include important viral pathogens such as hepatitis B and C. We also invite you to visit our new web site, which will include a listing of all our open studies. The web site is [www.AVRCtrials.org](http://www.AVRCtrials.org).

The AVRC move and name change coincides with the twentieth anniversary of the first clinical report of the AIDS syndrome. Many of us involved in HIV since the beginning have taken the opportunity to pause, and to reflect on the remarkable course of events that have unfolded over the past two decades. All of us remember the moment we were introduced to HIV, and none of us can forget the suffering we witnessed in the 1980s. As Kent Septkowitz chronicled in a medical historical perspective published in the June 7, 2001 issue of the *New England Journal of Medicine*, "although patients and physicians did their best, they were all just playing out the same grim script." For anyone who lived through this era, the remarkable entrée of HAART (Highly Active Antiretroviral Treatment) in the mid 1990s represented nothing short of a miracle.

During this time period, there was evolution in more than the therapies. In the same issue of *NEJM*, Dr. Michael Gottlieb provided a moving and personal perspective on how HIV has influenced our role as practitioners. HIV... "has taught us about the nature and diversity of love, about courage, compassion and caring. As a result of treating patients with HIV, many of us have matured into more skillful health care professionals than we might have otherwise been." Community activism also evolved during this time period, and was essentially redefined by courageous individuals affected by the HIV epidemic. Advocates for other diseases view HIV as a model of how to make a difference.

On this 20-year anniversary, it is fair to say that many have dismissed this moment of reflection as a sentimental waste of time. It is difficult to this day to accept the deaths, the discrimination, the isolation, the apathy, the judgment, the indifference, and the blame surrounding the epidemic. Despite the many advances, as Jeff Getty bluntly stated during an interview on 60 minutes, "HIV is not a simple, treatable disease for most of us." Sure, we are enormously grateful for treatment advances and for the dramatic reduction in opportunistic infections. But what about the body changes, the drug resistance, the dependence and the uncertainty surrounding optimal therapies? And what about the catastrophic effect of the global HIV epidemic?

As overwhelming as the current situation might appear, we would be in a much worse  
*(Continued on page 4)*

# Treatment for Reducing Insulin Resistance & Lipodystrophy

by Francesca Torriani, M.D.

Potent antiretroviral therapy has improved the general health of patients living with HIV infection. However, in the past years, patients have experienced side effects from anti-HIV therapy that have deeply affected their quality of life. These adverse effects include glucose intolerance and insulin resistance (conditions preceding diabetes of the adult and that may evolve into frank diabetes), high cholesterol and triglycerides, body composition changes (loss of fat in some areas of the face and the extremities, and fat deposition on the abdomen, hips and neck). At this time, the cause of these side effects and the long term consequences on the development of heart disease are unclear. Although, initially, protease inhibitors were thought to be primarily responsible for these changes, now all classes of antiretroviral drugs appear to be involved.

As HIV-infected persons live longer, the potential consequences of these laboratory and physical abnormalities are preoccupying patients and providers. Fat accumulation inside the abdomen (visceral fat accumulation) has been associated with insulin resistance in HIV-uninfected patients. In addition, insulin resistance appears to occur more often in HIV-infected patients with abdominal fat accumulation. So far, several treatments and strategies have been tried with little improvement of fat redistribution problems. Stopping or switching antiretroviral drugs appears only to slow fat redistribution without complete resolution. However, two types of drugs (metformin and thiazolidinediones) used to treat diabetes have been shown to reduce insulin resistance and fat accumulation in HIV-uninfected patients. Therefore, there is hope that these drugs might be effective in HIV-infected persons as well.

triglycerides, abdominal fat, and improved glucose tolerance after 16 weeks of treatment. In this study there were no cases of lactic acidosis, a severe, but rare adverse reaction to metformin. Because metformin is eliminated mainly by the kidneys (filtration and excretion), there is little or no concern for cytochrome interactions with antiviral medications.

Hadigan and collaborators studied the effects of metformin on fat redistribution and insulin levels on 26 HIV-infected subjects with fat redistribution and abnormal oral glucose tolerance test or hyperinsulinemia in a randomized double-blind 12 week clinical trial recently published in JAMA. Mean CD4 counts > 490 cells/mm<sup>3</sup> and HIV RNA < 6,000 copies/ml. Metformin treatment resulted in a significant reduction in the following, insulin AUC by 20%, weight and diastolic blood pressure. There was no significant change in lipid levels, except triglycerides which normalized. Although results from this trial are encouraging, it lacks generalizability because of the small number of patients studied, the lack of control for antiviral agents, the short treatment and follow-up intervals, the lower dose of metformin used, and the absence of significant liver or kidney disease.

## Metformin

Metformin has led to a reduction of insulin resistance and weight loss in HIV-uninfected persons. In patients with non-insulin dependent diabetes and central obesity, which is thought to be secondary to increased production of hepatic glucose, use of metformin is followed by a better control of glycemia. Studies have shown a reduction in hepatic glucose production rather than an increase in peripheral glucose uptake while on metformin. Also, the weight loss seen in these patients is essentially from fat tissue. Lastly, metformin decreases triglycerides and LDL levels by 10 to 20%. The reduction in triglycerides is thought to be due to a decrease in liver VLDL production.

In non-diabetic patients with fat distribution abnormalities, use of metformin results in decreased insulin levels, fasting glycemia, LDL-cholesterol, weight and waist-hip ratio. Lastly, a French proof of concept study in HIV-infected individuals demonstrated a reduction in

## Thiazolidinediones (TZDs)

(TZDs) improve the control of serum glucose by increasing peripheral insulin sensitivity. Two TZDs are FDA approved for use in non-insulin dependent diabetes mellitus (NIDDM): rosiglitazone and pioglitazone. Another TZD, troglitazone, was extensively studied and removed later by the FDA because of severe liver toxicity and deaths. TZDs improve glucose tolerance and insulin sensitivity in obese non-diabetic subjects and in women with a history of diabetes during pregnancy. In patients with non-insulin dependent diabetes, decreases in fasting glucose, insulin and hemoglobin A<sub>1C</sub> were

(Continued on page 5)

## Mission Statement

To develop and perform high-quality research protocols that enhance the overall management of HIV infection and other chronic infections while respecting and supporting the best interests of our clients. We maintain a safe, caring, and confidential environment.



## AVRC Updates staff:

**Diane Havlir, M.D.,** *Editor*

**Jack Degnan, M.P.H.,** *Managing Editor*

**Bruce Coon, R.N.,** *Layout & Design  
Proofreading & Production*

150 West Washington Street, Suite 100  
San Diego, CA 92103  
Phone: 619-543-8080  
Fax: 619-298-0177  
www.AVRCtrials.org

All rights reserved.

© Copyright August 2001

# **HIV and Adolescents** by Heidi Aiem and Mary Caffery, R.N.

## *HIV and Adolescents*

In the U.S. half of all new HIV infections occur in people under the age of 25. A recent survey in seven U.S. cities cited alarming rates of HIV among young urban men, especially African-Americans and Latinos. In this study, 41% engaged in high-risk sexual activities. In spite of the statistics, youth, like others have grown complacent about HIV. "It can't happen to me".

Most young people with HIV do not know that they are infected. Few test. Feeling invincible, many do not perceive the need. The majority of high-risk youth are not in primary health care where testing is offered. Others may be fearful, and are concerned about their parents finding out. Young people frequently lack information about testing, where to go and others face logistical and language barriers. Youth who test positive can also experience barriers as they seek care.

In response to need for local services, the UCSD Teen HIV program works closely with prevention and testing partners to promote developmentally appropriate and confidential HIV testing, and immediate referral to a rapid response adolescent HIV team. Coordinated by Larry Friedman, M.D. and Karen Loper, M.D., the UCSD Teen HIV Clinic provides comprehensive medical and social services from diagnosis. The "one-stop shopping" program assists youth by connecting them with primary care services; and also by providing emergency assistance, social support, and linkages with peers and community services. The program currently serves approximately 50 youth ages 12-24.

### *HIV Care during adolescence: instilling hope/providing support*

Bringing newly infected and newly diagnosed youth into HIV care can significantly impact their long-term health. The clinical course of HIV follows that of adults, yet with a few modifications. Initial findings from the REACH study (Reaching for Excellence in Adolescent Care and Health) suggest the potential role for the residual thymic function in immune reconstitution. Most youth enter care as asymptomatic with CD4 counts 400-500. HIV treatment guidelines are similar to adults although dosing needs to be based on physical development.

### *Youth respond to care*

HIV infected youth remain in care and benefit from intensive individually focused HIV care. They respond to care that is flexible, responsive, confidential and culturally appropriate. The UCSD Adolescent HIV team brings together expertise in HIV and an understanding of the developmental challenges of adolescence to help teens learn about and manage their HIV disease. The multidisciplinary team helps youth address their fears and concerns around HIV such as issues with disclosure to sexual partners and family. The team assists with the

development of skills in understanding and accessing HIV care, contraception and other primary health care needs. Psychosocial and counseling services are available to assist with mental health, substance use, school problems, and relationship issues.

### *Adherence*

Adolescents face many of the usual challenges adhering to medical therapy that the general population faces including complexity of medical regimen, lack of social support, adverse effects of treatment, distrust of health providers, lack of understanding about the medication and difficulty coming to terms with a life-threatening illness. The developmental capacities of adolescence can create even more complex barriers to adherence depending on their stage of development. For most adolescents, fear of disclosure of their HIV status to family, friends, and coworkers plays a major role in their ability to adhere to their medication regimen. Many youth would rather miss a dose rather than have to explain why they were taking medicine or otherwise disclose their status -- young people who live with their families but have not disclosed their HIV status are especially affected by this problem. As a result, many young people lack adult or peer support to reinforce their adherence. These same young people, who are also establishing independence, face conflict between needing to challenge authority figures and needing to depend on adult providers for support in adhering to medications.

Adolescents have difficulty adhering to a protease-containing regimen that has strict food and time requirements or side effects. This problem can become especially challenging on weekends when teens are away from their homes or are otherwise very active. Dietary restrictions or strict mealtimes for a young person can be difficult since teen lifestyles are usually not settled into daily or nightly routines. Side effects that may affect a person's appearance are a major concern for adolescents

*(continued on page 7)*

## **The AVRC would like to thank the following:**

**Abbott Laboratories  
Agouron Pharmaceuticals  
Boehringer Ingelheim  
Bristol-Meyers Squibb  
DuPont Pharmaceuticals  
Gilead Sciences  
GlaxoSmithKline  
Merck**

**for providing us with grants to cover the cost of production of the**

**AVRC Updates**

# A Promising New Antiviral: DPC 817

By Diane Havlir, M.D.

Increasing or even sustaining the gains for patients infected with HIV who are treated with antiretroviral therapy will require continued development of new agents that are active against drug resistant virus. These drugs may be among classes of drugs already in use in the clinic or may be among new classes such as "entry inhibitors" which disrupt different parts of the HIV life cycle. The nucleoside/nucleotide reverse transcriptase inhibitors were the first class of drugs approved for HIV treatment and remain critical components of current combination therapy. We have witnessed exciting results from studies of new NRTI drugs in development over the past year. One study of the NRTI tenofovir showed a .7 log reduction in HIV RNA when tenofovir was added to an existing regimen in treatment experienced patients. The NRTI DAPD has shown greater than 1.5 log reductions in treatment experienced patients.

At the AVRC, we are starting studies of a new NRTI designated as DPC-817. This compound is a cytidine analog that is active against wild type and mutant variants of HIV reverse transcriptase, including zidovudine (AZT) and lamivudine (3TC) resistant virus. Like some agents in its class, DPC-817 has a long intracellular half-life, estimated in the range of 13-17 hours. The bioavailability looks excellent in studies to date.

Our initial clinical trial is a phase I single dose study. This study will provide the first evaluation of pharmacokinetics of this drug in humans. Subjects will receive escalating single doses, and the disposition of the drug will be carefully monitored. Each dose will be separated by a period of at least one week. The intensity of the evaluations requires 3 visits, each lasting three nights, on the Clinical Research Floor of the UCSD Hospital in Hillcrest. Patients will be compensated \$600 for each hospital visit. Eligibility criteria

include no current antiretroviral therapy or other medications, CD4 cell counts above the threshold, or need for prophylaxis. If you are interested in this study or if you are a provider who would like to refer a patient, please call (619) 543-8080 and ask for the screening coordinator.

## **Learn more about HIV research. The AVRC Community Advisory Board meets monthly.**

### Upcoming Topics

**September 10th—Testosterone Gel  
and Metformin—2 different studies  
for abdominal fat**

**Meeting Place—150 W. Washington  
Meeting Time—5:30 PM**

**October 18th—ICAAC Conference  
Update (cosponsored by Being Alive  
and T.E.A.)**

**Meeting Place—Wyndom Hotel (call  
619-291-1400 for details)**

**Meeting Time—6 PM**

**For more information, call Jack or  
Gerry at 619-543-8080**

## **New Research Study for Cognitive Impairment**

Selegiline vs. placebo. All subjects offered drug after 24 weeks. Must be on stable anti-retroviral treatment or off treatment for 8 weeks. Study # A5090.

**Call 619-543-8080.  
Ask for the screening**

# Dear Readers

*(Continued from page 1)*

situation without the research advances made over the last decades. Basic science researchers discovered and taught us more about this virus than any other; vaccine development is now their charge. Epidemiologists defined the natural history of this disease; worldwide surveillance is the current priority. Clinical researchers taught us about the potency and limitations of antiretroviral therapy; testing new drugs and new strategies is our challenge. Outcomes researchers silenced the opposition to HIV care programs; global benefits of therapy now need to be highlighted. The advances of research are only realized through the skills of clinicians. We are privileged in San Diego to be home to clinicians on the cutting edge, who couple care with compassion. Over the years, they have saved the lives of thousands of patients; through skillful management of medications, toxicities and co-infections.

Perhaps the most important lesson we have learned over the last two decades was that efforts to prevent and treat HIV disease require the cooperation and support of the medical system, the community, the private business sector and the government. Research is not for everyone, but everyone benefits from research. As we move ahead to confront the issues before us, our research agenda features new areas such as Structured Treatment Interruptions (STIs), therapeutic vaccines, hepatitis C, therapeutic drug monitoring, treatment of metabolic complications and an international program. We remain committed to the development of new agents, salvage therapy and the study and understanding of drug resistance. We thank you for your collaboration in the past 14 years and look forward to working together in the years to come.

Sincerely,

# Insulin Resistance

(Continued from page 2)

observed after treatment with TZDs. In contrast to metformin, these drugs do not decrease weight or total body fat content, but patients with NIDDM experience a reduction in visceral fat accompanied by an increase in subcutaneous abdominal fat. If this is true, it could potentially be of great benefit to HIV-infected patients with lipid distribution abnormalities. Troglitazone has also been shown to decrease triglyceride levels, while increasing total cholesterol, LDL- and HDL-cholesterol. Lastly, because troglitazone has also been shown to reduce carotid intima thickness, a measure of atherosclerosis and the risk of coronary artery disease (CAD), it potentially could decrease the risk of CAD.

The metabolism of rosiglitazone is hepatic (glucoronization, CYP 2C8) but without inhibition of the major P450 enzymes involved in the metabolism of other antiretroviral drugs. However, no pharmacokinetic data is available with protease inhibitors or nucleoside reverse transcriptase inhibitors. Known side effects of rosiglitazone are anemia, and low white blood cells. Of more than 150,000 patients who received rosiglitazone, only two cases of liver toxicity have been reported. Because HIV-infected persons may be at higher risk for liver toxicity, anemia, low white blood cells and low blood glucose these laboratory tests will be very closely monitored during the study.

The combination of metformin and TZDs has been studied in non-HIV infected individuals and has shown additive effects (increased insulin sensitivity and better glucose control) and no additional adverse effects except for increased anemia.

## **ACTG 5082—New Study**

ACTG 5082 is a 32 week randomized, placebo-controlled, double-blind study of the efficacy and safety of metformin and rosiglitazone, alone or in combination, in HIV-infected patients with fat redistribution and fasting

hyperinsulinemia. Up to 128 men and 32 women will be enrolled nationwide. Eligible participants are HIV-infected adults who report fat distribution changes during the course of HIV infection and with an elevated waist-hip ratio, fasting insulin > 15 IU, with a plasma HIV RNA < 10,000 copies/mL on stable HIV therapy. Subjects must be on a stable antiretroviral regimen for at least 60 days prior to entry and not plan to change their antiretroviral therapy during the 32-week study. Exclusions are severe anemia (Hb < 9.1 g/dl for men, 8.9 g/dl for women), liver enzymes > 2.5 times the upper limit of normal (ULN), creatinine > 1.4 mg/dl, lactate > 1.5 times ULN, diabetes (i.e. fasting plasma glucose > 126 mg/dl, testosterone = 400 mg/dl for men not on testosterone replacement therapy, significant cardiac disease, use of antidiabetic medications, hormonal anabolic therapies, appetite stimulants, steroid therapy above replacement doses, immune modulators IL-2, interferons, pentoxifylline, thalidomide, niacin, hydroxyurea and cimetidine).

Before entering this study, participants will have an extensive history and physical examination, HIV RNA and CD4 counts, liver function tests and hematology, standard oral glucose tolerance test with glucose and

insulin measures. CT scan of the abdomen, DEXA and BIA will be performed prior to starting study. Participants will then be randomized in a double-blind fashion to one of either four arms: metformin (500 mg q12h oral for 14 days, then 1000 mg q12h oral) + rosiglitazone placebo, metformin placebo + rosiglitazone (4 mg oral once daily), metformin + rosiglitazone or metformin placebo + rosiglitazone placebo. After 16 weeks of study, all patients will be switched to open-label combination of metformin and rosiglitazone. The primary endpoints are changes from baseline to week 16 of fasting insulin, insulin AUC, visceral fat area as well as safety measures such as lactate, liver function tests, glucose, hemoglobin, renal function and symptoms such as diarrhea, nausea and vomiting.

ACTG 5082 will answer the very important question of how best to treat glucose intolerance and body composition changes. All patients will receive treatment and careful monitoring of the blood sugars, insulin, fat redistribution and lactate levels. Please call with referrals or for more information at the AVRC at (619) 543-8080.

## **Research Opportunities Online!**

**Check out the AVRC's new webpage!!!**

**The address is**

**[www.AVRCtrials.org](http://www.AVRCtrials.org)**

**Our new website is loaded with information about the AVRC, it's staff and the various research projects we are working on. You may also make a donation to HIV research through our website.**

## **Two Research Studies of Abdominal Fat Treatment**

1. Metformin vs. Rosiglitazone vs. combination
2. A5082 Testosterone Gel vs. placebo. All subjects offered drug after 24 weeks. – A5079 (men only)

**Both studies require HIV RNA less than 10,000.**

**Call 619-543-8080. Ask for the screening coordinator.**

# Research Studies for Multi-Drug-Experienced Individuals

- 1. Treatment Interruption Research Study** — A new treatment regimen is determined after resistance testing. Then, randomized to either: start new treatment immediately, or wait 16 weeks, off drug, before starting the new treatment. Must have multi-drug resistant virus. Must have CD4 count greater than 50 and HIV RNA more than 10,000. (*ACTG 5086*)
- 2. Treatment Intensification** — Add either abacavir or amprenavir + ritonavir to current regimen for patients with low level viral rebound. Previously must have had viral suppression while on current ARV regimen. Now must have an HIV RNA between 500 and 10,000 on the same regimen. No previous use of abacavir or amprenavir for more than 4 weeks. (*ACTG 5061*)
- 3. Salvage Research Study for PI, NNRTI experienced patients with treatment to include tenofovir** — Uses amprenavir + ritonavir + abacavir + another NRTI (based on phenotype results) + either tenofovir or efavirenz. CD4 count must be more than 50 cells/mm<sup>3</sup> and viral load >1000 copies/mL. (*PEARL*)
- 4. Salvage Research Study for PI experienced patients** — Compares two dosages of indinavir + ritonavir + 2 NRTIs. Must be naïve to indinavir and ritonavir. Viral load must be between 1000 and 50,000 copies/mL (*ACTG 5055*).
- 5. DAPD Research Study** — Adds DAPD (an experimental NRTI) to current regimen. Must currently be on antiretroviral therapy and have past experience with AZT/3TC or d4T/3TC. This is a Phase 1, 15-day study. Viral load between 5000 and 250,000 copies/mL. CD4 count must be more than 50 cells/mm<sup>3</sup>. (*DAPD*)
- 6. DPC – 817 (an experimental NRTI) Research Study** — A phase 1 research study – Participants take drug once up to three different study periods. Inclusion criteria: Currently off treatment for four weeks and remaining off for approximately 4 months. CD4 > 50. Study includes three 3-overnight hospital visits and payment up to \$1800.
- 7. High Dose ABT 378 (lopinavir) Research Study** — Evaluate escalating dosing of lopinavir/ritonavir in patients to see if protease inhibitor resistance can be overcome. Regimen includes lopinavir, ritonavir, and up to three NRTIs. Must have experience with at least two protease inhibitors and one NRTI. CD4 count must be less than 200 and viral load more than 100 copies/mL.

**For information on any of the above studies call the screening coordinator at 619-543-8080, or check us out at [www.AVRCtrials.org](http://www.AVRCtrials.org).**

## Cognitive Intervention Research Studies

- HIV is associated with cognitive impairment.
- 35% of asymptomatic and 50% of people with AIDS may experience symptoms.
- Some people who experience cognitive symptoms are failing on their current antiretroviral regimen.

**UCSD researchers are investigating the cognitive effects of physician-prescribed changes in antiretrovirals.**

Call Scott Holder at the HIV Neurobehavioral Research Center to find out more.  
619-543-5020

## Twice Daily, Non Protease Inhibitor Regimen For Treatment Naïve New Research Study:

Abacavir/3TC/AZT (Trizivir) + Efavirenz  
vs.  
Trizivir alone  
vs.  
3TC/AZT (Combivir) + Efavirenz

**Inclusion Criteria:**  
No experience with antiretrovirals  
HIV RNA > 400

Call 619-543-8080.

## HIV and Adolescents

(Continued from page 3)

cents because of the importance of personal appearance in young people, this as a result many youth stop taking their medications.

Factors that help a young person adhere to medical therapy are mutual decisions between the teen and the provider regarding treatment planning, building a trusting relationship with their provider, education about HIV infection and its treatment, addressing concrete basic needs and psychosocial needs relating to their life as well as their diagnosis. It is extremely important that teens are forgiven when they fail, they need to know that their medical team will continue to work with them even if they are not adherent. For information on programs for adolescents and/or research trials, contact the Adolescent HIV Program at 619-543-8080.



## *AVRC Updates*

AVRC (Antiviral Research Center)  
150 West Washington Street, Suite 100  
San Diego, CA 92103  
Phone: 619-543-8080  
Fax: 619-298-0177  
[www.AVRCtrials.org](http://www.AVRCtrials.org)

The *AVRC Updates* is published as a service to you. If you wish to have the *AVRC Updates* mailed to you, please fill out this form and send it to us, or visit us online. We will gladly put you on the mailing list to receive the *AVRC Updates* on a continuing basis. There is no charge to you for this service.

Name: \_\_\_\_\_

Address: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_\_ Zip: \_\_\_\_\_

**AVRC**  
**150 W. Washington St., Suite 100**  
**San Diego, CA 92103**

**Address Correction Requested!**  
**Please Do Not Forward!**