

# Is HAART Enough?

## An HIV Therapeutic Vaccine Study

by Susan Little, MD

Despite reports of durable virologic suppression among patients receiving potent antiretroviral therapies, sustained suppression has been associated with a gradual loss of HIV specific immune responses. Several strategies are under investigation to boost HIV specific immune responses in these patient populations, including therapeutic vaccination and structured treatment interruptions (STI). The rationale for development of a therapeutic HIV-1 vaccine includes the following:

1.) HAART is associated with variable success rates and a variety of adverse events with an unknown rate of long term toxicity;

2.) Latent reservoirs of replication-competent virus have very long half lives;

3.) Studies in humans and macaques suggest that cell mediated immune responses, including cytotoxic T-lymphocyte (CTL) responses, are important in the control of initial HIV infection and are associated with long term non-progressor status;

4.) HAART has been associated with gradual loss of HIV-specific CTL responses suggesting a role for viral antigen in driving the HIV specific immune response;

5.) Anecdotal data suggest a potential boosting of HIV-specific CTL responses (associated with relapse of viremia) following repeated cycles of STI among previously suppressed patients.

The UCSD Treatment Center is one of four sites nationally that has initiated a study to evaluate an HIV-1 gag DNA vaccine among HIV-infected subjects.

This study will determine whether

this plasmid DNA can boost previously low levels of HIV-specific CTL and potentially reduce HIV replication in study subjects. This vaccine has been extensively studied in several animal species (rodents and macaques) and is also under study in HIV-1 seronegative volunteers. Studies have shown plasmid DNA vaccines to be generally safe and capable of eliciting both antibody and CTL in primates. Macaques vaccinated with DNA and later challenged with pathogenic SIV all became infected, but with viral loads significantly lower than in controls or animals immunized with protein.

This study is a double-blind, placebo-controlled, dose-escalating study in HIV infected adults. Study subjects with CD4 cell counts  $\cdot$  500 cells/mm<sup>3</sup> and a documented history of complete virologic suppression (RNA < 400) for 24 months will be eligible. The primary objective of this study will be to establish the safety and tolerability of a four-dose schedule of HIV-1 gag DNA vaccine (1 mg and 5 mg per dose) in HIV-1 infected subjects. A secondary objective will be to evaluate cell-mediated immune responses to a panel of HIV peptides in vitro as measured by intracellular interferon gamma production. Approximately 48 subjects will be enrolled to receive either vaccine or placebo (3 vaccine to 1 placebo) by intramuscular injection at Day 0 and at weeks 4, 8, and 26. All subjects are expected to continue their antiretroviral therapy (ARV) during the two-year study period, though changes in ARV during study will be permitted according to accepted treatment guidelines. The study will proceed

see **Vaccine Study** on page 4.

### Mission Statement

To develop and perform high quality research protocols which enhance the overall management of HIV infection while respecting and supporting the best interests of our clients. We will maintain a safe, caring, and confidential

July 2000

Dear Friends,

We wanted to take the opportunity to share with you some exciting developments at the Treatment Center. At the end of June, our research center moved to a new location. We were at our former site in Hillcrest for over a decade. This site served us well and provided a convenient locale for many clients. But we needed more space to accommodate our expanding programs. We were fortunate to identify and renovate an office building at 150 W. Washington that meets our growing needs and allows us to remain in our Hillcrest home.

Our new location offers the advantage that it is within three blocks of the Owen Clinic and UCSD Medical Center. Both the adult and pediatric programs moved together and now occupy the first floor of the new building. Our longstanding collaborators at the HIV Neurobehavioral Research Center are situated on the second floor. The building has a lovely lobby and a large conference room for AIDS Clinical Rounds. We have a pharmacy on site as well as facilities for blood drawing and pharmacokinetic studies. There is ample patient parking next to the building, and metered parking is available for AIDS Clinical Rounds attendees on Washington Street.

Our research program continues to move ahead in many new directions. Strategies to prevent and treat drug resistant virus, metabolic complications of potent antiretroviral therapy, and measures to simplify therapy and improve adherence are at the top of the priority list. Important research focus areas include developing approaches to patients with primary HIV infection and patients co-infected with hepatitis B or C. Clinical trials of promising vaccines are underway, and shortly we will be starting a trial at the center to see if a vaccine can stimulate the immune response to patients already infected with HIV. We will continue to

*(Continued on next page)*

work with our industry collaborators to safely and swiftly bring new HIV therapeutic agents into clinical practice. In addition, we have the privilege of hosting three fellows in the coming year who will be focusing on various areas of HIV research. Dr. Denis Jones, pulmonary fellow, originally from South Africa, will be studying HIV and tuberculosis. Dr. Asok Kurup, will be visiting this year from Singapore and studying antiretroviral therapy. And Dr. Davey Smith, former chief resident at UCSD, will be studying HIV primary infection.

In the near future, we will be expanding our involvement in the arena of international health. The pediatric program already works closely with clinicians in Tijuana, and we will be putting efforts into establishing ties and setting up collaborations with other clinics around the world where HIV is exacting an unbearable toll. The World AIDS Conference in Durban, South Africa, in July, brought the grim realities of this global epidemic into the international spotlight.

Drs. Richman, McCutchan, and Spector founded our unit and continue as internationally recognized leaders in the field. Dr. Mathews and his staff at Owen Clinic set a standard for care and commitment to HIV-infected individuals that inspire us all. However, the progress, accomplishments, and growth of the Treatment Center are only possible because of the enormous support we receive from the community at large. Our HIV community providers have endorsed our research programs both in times of celebration and in times of bitter disappointment. HIV service agencies compassionately assist our clients, and our community advisory board has been an enormously important resource.

And our patients—we can never thank them enough! Their commitment, their perseverance, and their desire to participate in studies for the benefit of HIV-infected individuals is truly inspirational. They believe, as we do, that the effort of every individual can make a difference. As Margaret Mead once said, “Never doubt that a small group of thoughtful, committed citizens can change the world. Indeed, it is the only thing that ever has.”

We look forward to working with you in this new millennium in our new location. We will be forging new research frontiers, accepting new challenges, and confronting the HIV epidemic with renewed energy and enthusiasm.

Diane Havlir, MD  
Director, UCSD Treatment Center

## Vaccine Study *continued from page 1.*

in three stages, with each cohort of 16 subjects (3 vaccine to 1 placebo) evaluated for safety for at least 2 weeks following the second dose of vaccine (week 4) before the next cohort of 16 subjects is initiated. Both study participants and Treatment Center staff will remain blinded to vaccine or placebo assignment status for the duration of the two-year study.

Although there are no data to support it, there is a theoretical risk that vaccination with HIV-1 gag DNA will increase the viral load measurements of vaccine recipients. For this reason viral RNA and CD4 cell counts will be followed closely throughout the study. Study participant care providers will be contacted to determine if a change in antiretroviral therapy is indicated and if subsequent vaccinations should be administered if a subject has 2 consecutive viral RNA measurements of >1,000 copies/ml. Because DNA integration occurs naturally in all human cells, there is a very small chance of integration of vaccine DNA. Tests of large doses of HIV-1 gag DNA vaccine in animals have not shown a dangerous increase in the rate of DNA integration or the development of tumors.

Enrollment will be limited to 48 HIV-infected adults aged 18 to 55 who have a current CD4 cell count • 500 cells/mm<sup>3</sup> (and no CD4 cell count ever <200 cells/mm<sup>3</sup>) and a documented history of at least 24 consecutive months of both potent ARV therapy and undetectable levels of HIV RNA (<400 copies/ml measured at least every 12 to 16 weeks and < 50 copies/ml twice during those 24 months). Eligible participants must also have an HIV RNA <50 copies/mL at the time of screening to be enrolled. If you are interested in participating in this study or would like to refer a patient, please call the UCSD Treatment Center at 619-543-8080 to speak with the screening coordinator for further information.

We would like to thank the following:

**Abbott Laboratories**  
**Agouron Pharmaceuticals**  
**Bristol-Meyers Squibb**  
**Dupont Pharmaceuticals**  
**Merck**  
**Roche Laboratories**

for providing us with a grant for this and other editions of the UCSD Treatment Center News

## Merck Therapeutic Vaccine Study HIV-1 gag DNA vaccine

### Purpose:

To establish the safety and tolerability of this vaccine at 1 mg and 5 mg dosages.

### Inclusion criteria:

- 2 years undetectable and on antiretroviral treatment (RNA < 400)
- CD4 cells greater than 500 and never less than 200

Payment for participation: \$60 per visit, once enrolled.

**For more information  
call The Screening Coordinator  
at 619-543-8080**

## Cognitive Intervention 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 to find out more: (619) 543-5020

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## RESEARCH STUDIES AVAILABLE FOR ANTIRETROVIRAL-EXPERIENCED INDIVIDUALS

1. **ABT 378 (lopinavir) Study** — compares high-dose ABT 378 with standard dose ABT 378. Regimen also includes 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 1000 copies/mL.
2. **Combination Comparison Study** — uses amprenavir + ritonavir + abacavir + another NRTI (based on phenotype results) + either tenofovir or efavirenz. CD4 count must be more than 50 and viral load between 1000 and 50,000 copies/mL.
3. **Nelfinavir Failure Study** — 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*).
4. **Immune Enhancement Study** — adds GM-CSF to current regimen. Half receive placebo for the first 16 weeks. Must currently be on a stable 3-drug regimen. CD4 count must be less than 200 and viral load must be more than 1500 copies/mL.
5. **DAPD 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. CD4 count must be more than 50 copies/mL.

For information on any of the above studies,  
call the screening coordinator at  
(619) 543-8080

# Large Perinatal Transmission Study Closes

by Mary Caffery

PACTG 316 was designed to evaluate if a single dose of nevirapine given to the mother and to the newborn might further reduce the risk of mother-to-child HIV transmission during labor, over and above the standard medical and obstetrical management a woman receives during pregnancy. The NIAID Data Safety Monitoring Board reviewed the interim results of PACTG 316 on June 6, 2000. A total of 1404 women had been randomized to the study; 1194 had delivered; 1066 had been dispensed study drug, and infection status was available for 869 infants.

**DSMB (Data, Safety, and Management Board) Review and Comment.** No significant safety or toxicity issues have been seen in PACTG 316. However, the overall perinatal transmission rate was significantly less than the 5% hypothesized in the study, which would require at least a doubling in the number of enrolled patients to address the study's primary question. Additionally, a

significant proportion of transmission was antenatal (e.g., a positive DNA PCR at birth) as opposed to intrapartum, making it unlikely that the study would be able to detect an effect of a peripartum-only intervention, such as intrapartum/infant nevirapine. Therefore, the study will be unable to achieve the stated objective of detecting a 50% decrease in transmission with intrapartum/infant nevirapine.

The DSMB stressed that PACTG 316 continues to be a very important study. While the primary study objective cannot be met, the DSMB felt that blinded follow-up should be continued to obtain a single final analysis on the patients who have delivered to date. This follow-up is intended to monitor safety, evaluate infant HIV-infection outcome, and address additional secondary objectives of the protocol. Our thanks to all the patients, including the 22 from San Diego and to the health care professionals who participated in this study. Their commitment and dedication made this study possible.

## Adolescent Outreach Efforts Increased

by Mary Caffery

While the risk of acquiring HIV during adolescence remains high, few teens are tested for and seek care for HIV. Larry Friedman, MD, Karen Loper, MD, Brett Pickering, MD, Heidi Aiem and Mauricio Perez from the UCSD Mother, Child & Adolescent HIV Program participate in an evening mobile clinic offering STD/HIV testing for youth in Hillcrest, Downtown San Diego and Ocean Beach. In collaboration with Family Health Centers of San Diego and San Diego Youth & Community Services, this program improves access to youth sensi-

tive HIV testing. HIV infected youth are referred for care to the Adolescent HIV Program where they can receive primary medical care, supportive counseling, case management, health education and emergency assistance with transportation, food and housing.

The HIV Youth Council, a collaboration of HIV prevention and treatment providers has also stepped up outreach efforts countywide. For information on the van, adolescent services or HIV Youth Council contact Heidi Aiem or Mauricio Perez at 619-543-

## Obstetric, Pediatric Physicians Change

by Mary Caffery

**Mitchell Besser, MD**, the obstetrician for the UCSD Mother, Child & Adolescent HIV Program since 1991, recently moved to South Africa to continue his work in perinatal HIV. He is currently developing a program to provide clinical care and perinatal transmission reduction trials in Cape Town. The staff and community acknowledged his

dedication and commitment to the care of families and wish him well in his new endeavors.

**Andrew Hull, MD**, an Assistant Professor from the Department of Reproductive Medicine, Division of Perinatal Medicine, recently joined the UCSD Mother Child & Adolescent HIV clinical

see **Physician Changes** on page 7.

## HIV & TB Co-Infection Study

UCSD Treatment Center is conducting an observational study to better understand the co-pathogenesis of HIV and tuberculosis (TB) - "Viral and Immune Dynamics in HIV-Infected Patients with TB." To be eligible, patients must be receiving TB medications (for not more than 16 weeks), have a viral load of greater than 20,000 and are not yet on HAART. In this study, we are taking frequent blood samples before and after the initiation of HAART to try to understand how and if TB affects HIV replication. Patients must be treated with a regimen of nelfinavir and combivir initially, but the regimen can be adjusted as needed. The primary provider will continue to prescribe all medications and provide care for the patient; we will only be observing the natural history of these patients and comparing them to a matched control group without TB. For more information call the Screening Coordinator at 619-

## Physician Changes

continued from page 6.

care and perinatal research program. Dr. Hull brings extensive experience in the care of high-risk pregnancies. He practiced obstetrics in England and completed perinatology fellowships at Loma Linda and UCSD. Dr. Hull will provide perinatal consultations, comprehensive prenatal care and clinical trials to monitor the safety and tolerance of antiretrovirals during pregnancy and their role in the reduction of vertical HIV transmission. For further information on HIV and pregnancy, perinatal studies, or to refer a patient, please call Patricia Franklin, CFNP at 619-543-8080.

### TENOFOVIR RESEARCH STUDY FOR TREATMENT NAÏVE INDIVIDUALS

Tenofovir + 3TC + efavirenz  
vs.  
d4T +3TC + efavirenz

#### Inclusion criteria:

- Treatment Naive
- HIV RNA > 5000

Call (619) 543-8080.  
Ask for the Screening Coordinator

### Research Study:

## Switch Regimens

in individuals with Metabolic Disorders  
(CCTG 577)

### Study Design:

Stay on same regimen or switch to efavirenz (same NRTIs).

### Inclusion Criteria:

- ◆ Currently having metabolic complications
- ◆ Currently on Protease Inhibitor with 2 NRTIs;
- ◆ HIV RNA < 50

Call the Screening Coordinator  
at 619-543-8080

### Treatment Center News

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