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<i>Inside this issue:</i>	
Title of article	pg#
Boosted PI Regimens	1
Vaccine Study	1
Neuropathy	2
HIV pts in ICU	2
Adolescent Trials Network	3

Mission Statement

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

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Boosting Protease Inhibitor Regimens

by Richard Haubrich, MD

As the number of patients with resistant HIV strains has increased, so has the need to accurately use and interpret resistance assays. Phenotype assays provide information on how individual drugs would be expected to inhibit a particular strain of HIV. In these assays, the concentration of drug needed to inhibit 50% of virus growth (IC₅₀) from a patient sample is compared to the concentration needed to inhibit growth of a non-resistant (control) virus strain. The ratio of the numbers, the fold change in IC₅₀ (FC), is the metric used to determine drug susceptibility. In order to best use the phenotype information, we need to know the FC which best predicts the clinical response to a specific drug.

For each drug, the FC that predicts activity, termed the clinical cut-point, is different. Researchers at the UCSD AVRC are trying to help define these clinical cut-points.

Essential to the interpretation of the FC cut-point is the concentration of drug achieved for each patient. The FC cut-points for the protease inhibitors will be different when the Protease Inhibitors (PIs) are boosted with ritonavir. Thus, in order to obtain the most information from the phenotype assay, the actual (or expected) concentration of PI should be compared

(continued on page 5)

Therapeutic Vaccine Study

by Susan Little, MD

The importance of HIV-specific cytotoxic T lymphocytes (CTL) in controlling HIV viral replication is based upon indirect, albeit persuasive studies demonstrating an association between control of viral replication and vigorous HIV-specific CTL responses directed toward a variety of HIV-specific peptides. Significant HIV-specific CTL responses are typically observed in the setting of acute HIV infection and are temporally associated with the decline of viral load (10 to 200 fold) during this period. In contrast, among patients beginning potent therapy in the setting of chronic HIV infection, these CTL responses are typically lower and wane over time, perhaps resulting from more limited antigenic stimulation associated with sustained virological suppression. Although potent therapy controls viral replication in most individuals, it does not appear to significantly reduce the size of the la-

tently infected cell reservoir, such that lifelong treatment with available therapies is currently envisioned. Therapeutic vaccination is an immunologic intervention aimed at augmenting the HIV-specific immune response such that an ongoing and potent immune response will affect these reservoirs of viral persistence. Furthermore, persistence of an effective HIV-specific immune response might ultimately permit modification of current treatment guidelines to limit the use of antiviral medications.

The UCSD Antiviral Research Center is participating in a multicenter, phase I study (Merck 014) to evaluate the safety, tolerability, and immunogenicity of an adenovirus serotype 5 vector (MRKAd5) HIV-1 gag vaccine in HIV infected adults with sustained virological suppression. The study design is a double-blind,

(continued on page 5)

Neuropathy: New Research Questions

by Ron Ellis, MD

The most common neurological condition for which individuals with HIV infection care is distal, symmetrical polyneuropathy (DSPN). A new study (ACTG A5117: "A Pathophysiologic Study of Development of Distal Symmetrical Polyneuropathy in Individuals with Advanced HIV-1 Infection and Prior Antiretroviral Exposure,") reflects physicians' recognition that the specific causes of this disorder are unknown, a fact that continues to thwart the development of effective therapies and prevention strategies.

Individuals with DSPN seek treatment principally because of sensory disturbances, variably described as stabbing pain, burning, aching, numbness or "pins-and-needles" sensations in the toes and feet, which make it difficult to walk and frequently interfere with sleep. DSPN can be related to treatment with certain antiretroviral medications (dideoxynucleoside reverse transcriptase inhibitors) or simply to HIV infection itself. Contrary to expectations, however, discontinuing the offending antiretroviral drugs, or effectively treating HIV by reducing viral load, does not eliminate the symptoms or signs of the disorder. The goals of A5117 are to identify factors that lead to the development or worsening of DSPN, and to test the hypothesis that DSPN is related to abnormal functioning of mitochondria, the cellular organs that provide energy to sensory neurons, and indeed to all cells in the body.

Individuals eligible for participation

in A5117 will have a current CD4 count less than 300, and have received any type of antiretroviral therapy, past or present, for at least 15 consecutive weeks. A5117 is not a treatment study, so there is no direct benefit to participants, with the exception of reimbursement for participation. However, the study offers an opportunity to help determine the underlying causes of DSPN, the first step towards better treatment and prevention in the future.

Participants will agree to undergo a series of neurological evaluations, and will provide blood as well as two superficial skin samples from the legs.

To refer a patient, or to find out more information about this study, contact the AVRC screening coordinator at (619) 543-8080.

HIV Positive Patients in the Intensive Care Unit

by Denis Jones, MD

While the success of HAART has drawn attention away from the study of seriously ill patients and those with opportunistic infections, there remain a significant number of HIV-infected individuals hospitalized in the intensive care unit (ICU) each year. In areas with a high prevalence of HIV infection as many as 30% of the patients admitted to the ICU have underlying HIV infection. The most commonly encountered problems are respiratory failure, sepsis and neurological dysfunction with the overall mortality ranging from 50% - 70%.

A5141 is a multi-center study designed to evaluate whether patients

with AIDS who are admitted to an intensive care area with an acute opportunistic infection, pneumonia or sepsis will benefit from the early initiation of antiretroviral therapy.

Patients will be randomized to receive either standard intensive care management together with 4 weeks of HAART or standard treatment alone. After the first 4 weeks of the study patients who are receiving HAART can elect to: continue with antiretroviral therapy, stop antiretroviral therapy or change to an alternate regimen. Those patients who were randomized to no antiretroviral therapy can then elect to

(continued on page 3)

Twice Daily, Non Protease Inhibitor Regimen For Treatment Naïve

New Research Study: A5095: *Abacavir/3TC/AZT (Trizivir) + Efavirenz*

vs.

Trizivir alone

vs.

3TC/AZT (Combivir) + Efavirenz

Inclusion Criteria:

No experience with antiretrovirals

HIV RNA > 400

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Ask for the screening coordinator.

HIV Positive Patients in ICU

(continued from page 2)

start therapy and all patients will be followed for 6 months.

Those patients randomized to receive HAART will receive a 4-drug regimen (zidovudine, lamivudine, efavirenz and nelfinavir), which will be provided by the study for up to 6 months. Modifications of the initial treatment regimen are permitted at any time during the study.

At this time only adult patients

with limited prior antiretroviral exposure who are admitted to one of the UCSD hospitals will be eligible for the study.

The primary goal of this study is to determine if early antiretroviral therapy is associated with a decrease in mortality after 4 weeks of therapy. In addition, the study will examine the effect of immediate HAART on: ventilator free days, length of ICU and hospital stay and the incidence of nosocomial

infections. The study will also examine the effect that critical illness may have on the absorption and metabolism of antiretroviral agents.

As part of A5141, a sub-study (A5162) will determine if the early initiation of HAART has any effect on the treatment and clearance of pneumocystis pneumonia.

The Adolescent Trials Network Offers Treatment Opportunities for Today and Hope for the Future

by Mary Caffery, RN, MSN

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 youth, especially Latinos and African Americans. The latest studies in the San Diego/Tijuana region document high rates of HIV infection among 20-25 year olds. The most common mode of transmission among male and female youth is sexual risk, primarily sex with men. Early sexual activity, multiple partners, older more experienced partners, low condom use and high rates of sexually transmitted diseases combine to place youth at increased risk for acquiring HIV.

In response to national concerns over HIV risks for teens, the National Institute of Child Health and Human Development collaborated with the National Institutes of Drug Abuse, Mental Health and Alcohol Abuse and Alcoholism to develop an Adolescent Medicine Trials Unit of HIV / AIDS Intervention. Launched in 2001, the Adolescent Trials Network (ATN) has 15 sites in the U.S. and Puerto Rico. The ATN is designed to work with other NIH research networks to pro-

duce interventions that impact HIV treatment and behavioral strategies to prevent HIV infection among youth. They are also working to develop and eventually distribute an HIV prevention vaccine. The ATN leadership is working closely with researchers, clinicians, youth and a community advisory board to ensure that vaccine research in youth is done within a broad and sustained community prevention effort.

The UCSD Adolescent HIV Program was selected to be one of the 15 ATN in 2001 and is currently linking with community partners to assess high-risk youth, define local demographics, identify and mobilize community resources. Current efforts are designed to estimate the incidence of HIV infection in high-risk populations, monitor health outcomes of risk behaviors, and identify and help youth access care. HIV positive and high-risk youth are also invited to participate in a long-term study to monitor risks, behaviors and health status. The San Diego ATN consists of a youth friendly team of researchers, clinicians, nurses, outreach workers and peer advocates. Please contact Lisa Stangl, NP at 619-543-8080, for additional information on the ATN.

The AVRC would like to thank the following:

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**AVRC
Updates**

***Will a 16-week Treatment Interruption Benefit Patients
who have Multi-resistant Virus?***

A5086 is a study to answer this question.

- 1. Subjects receive phenotype and genotype testing.**
- 2. The best possible regimen is determined based on resistance testing, researcher, and primary provider decision.**
- 3. Subjects are randomized to either start the new regimen immediately, or wait 16 weeks off treatment, before starting the new regimen.**

Inclusion Criteria:

- HIV RNA > 5000**
- Currently on Antiretroviral Therapy**

Call 619-543-8080.

Ask for the screening coordinator.

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**

Research Opportunities Online!

**Check out the
AVRC's webpage!!!
www.AVRCtrials.org**

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

Therapeutic Vaccine

(Continued from page 1)

placebo-controlled, dose escalating study in subjects who have a documented history of undetectable levels of HIV-1 RNA (<500 copies/mL) for a minimum of 12 consecutive months while receiving a potent antiretroviral regimen, and have a CD4 cell count ≥ 500 cells/mm³ (with no prior CD4 cell count <200 cells/mm³ within 12 months). Patients must also be negative for hepatitis B surface antigen and antibody to hepatitis C virus. This study provides an opportunity for volunteers meeting the entry criteria to help in the development of an HIV vaccine. Because this is a blinded study, immunogenicity results will not

be provided until after the study is completed and all patients will be expected to continue their antiretroviral medications during the entire study period. Study volunteers will be reimbursed for their travel time and possible inconvenience of study participation.

If you are interested in participating in this study or would like to refer a patient, please call the UCSD Antiviral Research Center at (619) 543-8080 to speak with the screening coordinator for further information. We are actively recruiting for this study and anticipate that we will be able to offer study participation to approximately 10 subjects.

Boosting PI regimens

(continued from page 1)

to the IC₅₀. This new metric, the inhibitory quotient (IQ) may be a better predictor of response to a boosted PI regimen.

A new study at the AVRC will be closely evaluating the utility of the IQ to predict response to a boosted PI regimen. A5126 is a randomized, open-label study of the predictive value of pharmacokinetic (PK)-adjusted phenotypic susceptibility (C_{12hour}/IC₅₀, IQ) on antiretroviral (ARV) response to ritonavir (RTV)-enhanced protease inhibitors (PIs). Patients who have been on all three classes of agents (PI, NNRTI and NRTI) and are currently failing a PI regimen will be eligible for the study. At screening, a phenotype assay will be done and patients will be randomized to receive a new baseline ritonavir boosted regimen with either indinavir (IDV), GW-433908 (a new pro-drug of amprenavir), or lopinavir (LPV). The randomization will be dependent on the PI in the current regimen (i.e. will be partially selective), so that a patient currently on lopinavir will not be randomized to the same

treatment they are currently taking. The only change for the first 2 weeks of the study will be the PI regimen. After 2 weeks, drug concentrations (PK profile) will be done and tenofovir will be added in addition to other changes to the regimen, based on the phenotype. Patients will be on study for 24 weeks.

The main objective of the study is to evaluate the correlation between the IQ ratios (C_{12h}/IC₅₀) for each protease inhibitor (PI) and the short-term antiretroviral activity (measured by change in HIV-1 RNA from baseline to day 14) of the PI combined with ritonavir (RTV). Additionally the IQ will be compared to the 24-week response. The study is unique in that the IQ ratios will be calculated using the same method for 3 important PIs used in the salvage setting. Previously, this metric has been evaluated for each drug separately using different methods. This study will have a major effect on the ability to select a PI in the salvage setting.

For more information about this study, call the AVRC screening coordinator at (619)543-8080.

Learn More About HIV Research at UCSD

The AVRC Community Advisory Board Meets the first Monday of each month.

Learn from the researchers and let the researchers hear from you.

Call 619-543-8080 for more information.

Comparing Boosted Protease Inhibitor Regimens ACTG 5126

After phenotype testing, subjects switch from current PI to either: indinavir/ritonavir or lopinavir/ritonavir or amprenavir/ritonavir. All will add tenofovir.

Inclusion Criteria:

- **HIV RNA > 5000**
- **Experience with all 3 drug classes**
- **Currently on a protease regimen**
- **Not on nelfinavir as only protease inhibitor.**
- **Not on delavirdine.**

**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. HIV RNA more than 5,000. (A5086)
- 2. Comparing Ritonavir-enhanced Regimens** — After phenotype testing, subjects switch from current PI to either Indinavir/Ritonavir or Lopinavir/Ritonavir or Amprenavir/Ritonavir. All add tenofovir. HIV RNA must be more than 5000 copies mL. Must have experience with all three drug classes. Must currently be on a protease regimen. Must not be on Nelfinavir as only PI and must not currently be on Delavirdine. (A5126)
- 3. 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 one drug from each class. HIV RNA must be more than 1000 copies mL. No limitations to enrollment based on CD4 criteria. Okay to be off therapy at time of enrollment to study.

For information on any of the above studies call the screening coordinator at 619-543-8080, or check us out at www.AVRCtrials.org.

New Research Study for Cognitive Impairment

Selegiline vs. placebo.
All subjects offered drug after 24 weeks.
Must be on stable antiretroviral treatment
or off treatment for 8 weeks.

Study # A5090.

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

Two Research Studies of Abdominal Fat Treatment

- Metformin
vs.
Rosiglitazone
vs.
Both
(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.**

We invite you to join us in
SummerQuest 2002

**Presented by Rob Appel's "Dance Electric"
a fundraiser for AIDS Care and Research**

This year, the **AntiViral Research Center (AVRC)** is
one of the recipients of this event
along with the Asian Pacific Islander Community AIDS Project (APICAP).

"Dance Electric" will include leading Southern California dance companies, Broadway-style vocalists, and special guest stars to be announced.

Also, the "Spirit of The Quest" award this year will be given to the director of the AVRC,

Dr. Diane Havlir

and will be presented by County Supervisor Pam Slater.

The Event takes place on Saturday, **June 8th** at 6pm at the
Spreckles Organ Pavilion Main Stage in Balboa Park.

Tickets prices: \$250—VIP Ringside Tickets; \$125-Preferred Dinner seating;
\$25-General Admission (Show only)

For more information, call Appel Presents at (619) 665-9730

AVRC Updates

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