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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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A Letter from Diane Havlir, MD: former director of the AVRC

Dear Readers,

I would like to let you know that I am leaving the AVRC and have accepted a position as the Director of the HIV Programs at San Francisco General Hospital as of July 1, 2002. This position represents an exciting opportunity to continue work in HIV care and research both locally and internationally at University of California, San Francisco where I received my training in Internal Medicine nearly 2 decades ago.

I would like to thank you for many years of support and participation at the AVRC. One of the highlights of my 12 years at University of California, San Diego has been working with physicians and health care providers who both provide outstanding clinical care and who contribute to research efforts. The atmosphere of mutual respect and support that exists among HIV clinicians and researchers in San Diego has enabled those infected with HIV to be the first to benefit from the many research advances we have seen over the last decade. I particularly would like to thank Dr. Chris Mathews, an inspiration to me and the entire community of HIV care providers.

I would also like to thank the many patients who have participated in our research studies. Your courage and commitment has made a difference for the many persons living with HIV disease. The world AIDS conference in Barcelona reminded me that we are a diverse global community with a common cause

to fight HIV. I will continue to work with you with enthusiasm and determination as a part of this global effort to prevent and treat HIV disease.

I wish you and the San Diego community the best in the coming years to support and advance the care of those living with HIV.

Sincerely,

Diane V. Havlir, MD
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Integrase Inhibitors—a New Class of Drugs

by Ramzi Asfour, MD, Richard Haubrich, MD, and Susan Little, MD

As the number of patients with acquired or transmitted HIV drug resistance increases, the need for drugs with novel mechanisms of action and antiviral activity against pre-existing drug resistant variants is more urgent. Several novel drug candidates that target HIV-1 integrase have been evaluated in preclinical studies, though there are no currently FDA-approved drugs in this class. Because of their unique mechanism of action, integrase inhibitors show good antiviral activity against most drug resistant variants in preclinical studies. Several different HIV-1 integrase inhibitors are now entering clinical development.

HIV-1 integrase is one of three enzymes required for viral replication and catalyzes the integration of viral derived DNA into host chromosomes. Infectious viral particles contain 2 strands of RNA, as well as the viral proteins, integrase and reverse transcriptase. Reverse transcriptase catalyzes the synthesis of viral DNA from RNA resulting in double stranded viral DNA. HIV integrase performs the necessary splicing and joining functions that allow integration of the viral DNA into the host DNA. A number of new compounds that target the HIV integrase are in development. The UCSD AVRC will be performing two studies of different HIV-1 integrase inhibitors.

The first study will examine S-1360, a compound developed by Shionogi-GlaxoSmithKline Pharmaceuticals that inhibits an HIV strand transfer step of viral integration. It has activity, in cell culture models, against wild-type as well as drug resistant HIV. Three studies in people have been done to date. The first two were safety studies in HIV-negative, healthy volunteers of single and multiple doses of S-1360. They demonstrated that the most common side effect related to study medication was headache. A study in HIV infected patients was recently completed, but results are pending.

The S-1360 integrase study at the

AVRC will be in treatment naïve, HIV-positive subjects. S-1360 will be given for 10 days. The major objectives are to evaluate activity against HIV and to determine the concentration of S-1360 attained in the blood stream. The study will then be able to evaluate the relation between the concentration of S-1360 in the blood and activity against HIV. The study will also evaluate the safety of the compound.

A second integrase study will be conducted by the AVRC to study a Merck Integrase inhibitor, L-870810. L-870810 functions by blocking a critical DNA strand transfer step of HIV-1 integration. L-870810 is highly selective for HIV-1 integrase with >1,000 - 10,000 fold activity against viral integrase compared to other phosphotransferase enzymes.

Data from phase 1 clinical trials of single and multiple dose L-870810 in HIV-negative, healthy volunteers, suggest that L-870810 is safe and very well tolerated. There have been no serious adverse effects related to the study medication. In a 16 day oral toxicity study in dogs, there were some minor histopathological changes in liver and kidney specimens at autopsy in animals treated with higher doses than are being evaluated in human subjects. These changes were not associated with any abnormality of serum or urine biochemistry. Additionally, L-870810 appears active against multi-drug resistant isolates, is synergistic with currently available ARV's, and is associated with a 1 to 3 log decrease in viral load in a rhesus macaque model. L-870810-resistant mutants have been very difficult to select *in vitro*, following up to 2 years

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Twice Daily, Non Protease Inhibitor Regimen For Treatment Naïve Patients

(Research Study #ACTG 5095)

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.

Ask for the screening coordinator.

Diverse Participation in HIV Research

by Allen Gifford, M.D.

To do the best possible job of representing the communities actually affected by HIV, clinical research should enroll diverse populations of patients, including people of color, and women. While the AntiViral Research Center (AVRC) has always made extra efforts to recruit minorities in HIV research, doing a good job of study enrollment is difficult. A team led by AVRC researcher Dr. Allen Gifford, recently found that nationwide, African-Americans and Hispanics were about half as likely to participate in HIV treatment trials and have access to experimental medications as non-Hispanic whites. This study, a comprehensive analysis of data from the HIV Cost and Services Utilization Study, interviewed 2864 persons representing 231,400 adults on three occasions between 1996 and 1998. The results are detailed in the May

2 issue of the *New England Journal of Medicine*.

Non-Hispanic whites accounted for 44 percent of reported AIDS cases and 49 percent of HIV-infected patients receiving treatment, but made up 62 percent of those in HIV medication trials. They were also more than twice as likely as African-American patients to try to obtain an experimental medication, and were slightly more likely to succeed. Among patients who said they actively sought out experimental drugs, 77 percent of non-Hispanic whites and 69 percent of African-Americans received them. African-Americans accounted for 37 percent of reported AIDS cases and 33 percent of HIV patients in care, but made up 23 percent of those in medication

trials. Hispanics accounted for 18 percent of AIDS cases and 15 percent of HIV cases in care, but made up 11 percent of those in medication trials. These first nationwide data from HIV/AIDS patients show that many HIV/AIDS patients do access experimental treatments, but documents a relative lack of success in enrolling minorities into clinical trials.

This study indicates that non-Hispanic white patients, men who had sex with men, those with higher incomes, higher levels of education or private health insurance and those who received care closer to a clinical-trial center were all more likely to have received experimental medications at some point while receiving HIV care. The lack of representation in trials is important because many patients with serious

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Integrase Inhibitor Studies

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of passage in tissue culture. The strains that did develop resistance were notably less replication competent and remained susceptible to available NNRTI's, PI's, and NRTI's. L-870810 does not appear to rely upon P450 metabolism, which may reduce possible interactions with other available antiretroviral drugs.

The UCSD Antiviral Research Center, in collaboration with Merck Research Laboratories, is participating in a multicenter, phase Ib study (Merck Integrase 004) to evaluate the safety, tolerability and effectiveness of L-870810 in HIV infected individuals. This will be the first evaluation of this drug in HIV infected individuals. The study is a double blind, randomized, placebo-controlled trial in patients who have stable viral loads (plasma RNA must be > 10,000 copies/ml) and are treatment naïve or have been off all antiretroviral medications for at least 3 months at the time of study entry. Patients must be

hepatitis B antigen and C antibody negative. Study participants will receive 400mg L-870810 by mouth twice daily for 10 days and will be monitored closely.

It is not expected that study participants will benefit directly from administration of either study, given the short duration of the study. They will be reimbursed for their travel time and the possible inconvenience of study participation. If you are interested in these studies, 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 and anticipate that we will be able to offer study participation to 5-10 subjects for the S-1360 study and approximately 4 subjects for the L-870810 study.

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 delavirdin e.**

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

Adherence: A Factor Critical to the Success of HAART

by Glen Wagner, PhD and Richard Haubrich, MD

The current success of antiretroviral treatment strategies has been tempered with the reality that strict adherence to therapy is needed to maintain the effect. Acute and chronic toxicities have further burdened patients and their providers and complicate the adherence goal. Antiretroviral therapy can only be successful if patients adhere to the medication regimens. A study by the CCTG, published in 1999, was one of the first to document that reduced adherence, measured by a self reported questionnaire, lead to lower suppression of viral load levels. Lack of adherence is also a major public health concern since poor adherence leads to viral breakthrough and ultimately viral resistance. If resistance to one protease inhibitor develops, full or partial cross-resistance to other protease inhibitors may occur. Thus, poor adherence could reduce the utility of classes of antiretroviral agents as treatment options for the individual and perhaps for any persons he or she may subsequently infect. This link is substantiated by the recent documentation of the transmission of multidrug resistant strains of HIV.

It is not yet known what level of adherence is needed for successful treatment, but many clinicians believe that

95% is what's needed for optimal treatment benefit. For a person taking medication twice per day, that would mean missing fewer than one dose per week. The relationship between adherence and clinical outcome is not a simple one, as factors other than adherence contribute to whether or not a patient improves with treatment (e.g., presence of resistant virus prior to onset of treatment; malabsorption of medication; altered drug metabolism).

ADHERENCE INTERVENTIONS

Review of the general medical literature reveals no established methods for assuring adherence to any medication regimen. While many studies have been conducted looking at interventions to improve patient use of medications for chronic disease, research on interventions to improve HIV antiretroviral adherence is rare. Only a small number of controlled adherence intervention studies have been conducted. Most have multiple components and are usually based on a cognitive-behavioral model. In general, the empirical findings of these studies reveal a relatively modest effect. In a review of the adherence intervention literature, researchers identified 13 ran-

domized clinical trials that included comparison groups, measures of both treatment outcome and adherence, and at least 80% retention over 6 months. Less than half of the interventions resulted in improved adherence. Some interventions improved adherence but had no clinical effect; others improved clinical outcomes but had no effect on adherence.

The available data, together with theoretical models applied to adherence behavior, suggest that multiple strategies, rather than information and education alone, are most successful in improving adherence. Intervention components likely to be effective include tailoring the regimen to the person's lifestyle; teaching self-monitoring skills; identifying barriers to adherence and improving

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Cognitive Intervention

- 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.

Diverse Participation in Research

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diseases have few or no options for conventional treatment, so enrollment in trials of experimental treatments or new applications of existing medication can be their only means of accessing needed care. Also, because a drug's effects can vary by gender or race, doctors like to have women and minorities included in the studies to determine whether an experimental drug works selectively. The study found that nationwide, women were just as likely to be included in HIV research trials as men were.

The reasons for the gap in access to HIV medication trials are as com-

plex as the epidemic itself. The explanations may range from patient biases against research, fostered by the legacy of racist experiments in the early 20th century, to physician biases regarding which of their patients are most likely to take their medications.

The urgency of expanding the pool of AIDS drug study participants extends beyond the potential benefits for individual patients. Having a skewed trial population could also affect the scientific merit of drug studies. To best understand how medicines work and how they don't, researchers need participants who reflect the breadth and diversity of the epidemic.

Adherence

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problem solving skills to generate solutions to these barriers; reframing beliefs and attitudes about treatment; improving adherence self-efficacy; and facilitating positive social support for adherence. These psychoeducational intervention components have been used to successfully change behavior in other areas such as HIV risk behavior reduction.

ADHERENCE STUDY

CCTG 578 is an ongoing study designed to evaluate 2 methods to improve patient adherence to antiretroviral therapy compared to the standard of care given in the clinic. Patients who enter the study are randomized to either of two adherence interventions versus no intervention. Both interventions include HIV educational training and examination of past medication-taking experiences to help identify ways to improve future adherence. One arm of the intervention also includes a two-week placebo training with an electric monitoring medication cap to identify potential problems prior to starting a new regimen.

The objectives of CCTG 578 are to evaluate if one of the two interventions significantly improves adherence at week 4 compared to no intervention, to define if the effect of improved adherence is long lasting (up to week 48), and to see if improved adherence improves response to antiretroviral treatment. For those randomized to an intervention, five sessions are scheduled to provide training and/or practice aimed at improving adherence. Models of primary prevention suggest that it is better to prevent problems of poor adherence rather than to try correcting or eliminating such patterns once they have developed. Three of the five sessions of the intervention take place before treatment is initiated, during which the patient focuses

solely on developing the skills, motivation, and self-efficacy needed to adhere well, without the distractions and complications related to side effects that are common in the initial days and weeks of treatment. Focusing the 2-week period exclusively on adherence may reinforce for patients the importance and need for optimal adherence, thereby increasing their motivation and commitment to adhere. Moreover, social psychological research on “the foot in the door” effect suggests that patients induced to work on adherence prior to starting therapy will see themselves as more committed to adherence and will therefore devote more effort to adhering to their regimen once therapy begins.

CCTG 578 also will assess the relative efficacy of a practice trial with inert medication in improving adherence to the actual regimen once it is started. The practice trial with inert medicine is the key ingredient of the proposed training intervention, and it is the practice trial component that makes the training intervention unique and distinct from all other interventions that are currently being evaluated. The potential benefits of the practice trial include: 1) providing patients with a “real life” context in which to experience what adherence to the regimen will entail and how it will affect their daily routine and lifestyle; 2) providing concrete experience (rather than simple mental imagery) from which patients can identify problems that need to be addressed to facilitate optimal adherence; 3) bolstering patients’ confidence in being able to follow the regimen (self-efficacy) if they adhere well during the practice trial. If they do not adhere well during the practice trial, the difficulties they encounter can be used in the intervention to motivate them to address the barriers to adherence during the remaining intervention sessions.

DRUG MONITORING

Since CCTG 578 is integrated with a therapeutic drug monitoring component, it will potentially answer other important questions for clinical management of HIV in addition to the effect of the adherence intervention. Examples are: How are various levels of adherence associated with likelihood of optimal clinical outcome (undetectable viral load)? What level of

poor adherence significantly increases the likelihood of viral mutation and resistance? How is adherence correlated with drug concentration levels? In addition, we will use the data collected to calibrate a structural model of the relationship between adherence and clinical outcome, which could then be used to predict the viral load and CD4 count trajectory for patients prior to treatment onset and according to various levels of adherence.

People interested in more information about CCTG 578 should call the screening coordinator at 619-543-8080.

Therapeutic Drug Monitoring (TDM) and Adherence Research Study

for HIV positive people who are planning to start a new (or first) treatment regimen.

Study Design:

TDM *vs.*
adherence assistance *vs.*
TDM + adherence assistance
vs. neither.

HIV RNA must be above
3000 to qualify.

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

Kaletra in Cerebrospinal Fluid

by Scott Letendre, M.D.

Combination antiretroviral therapy has reduced the incidence of HIV-associated dementia (HAD) by approximately 50% since 1996 [1]. This reduction has improved the quality of life of people infected with HIV but several recent findings indicate this benefit may be limited. For example, HAD seems to be occurring earlier in disease [1], the prevalence of HIV encephalitis at autopsy has not declined [2], and severe forms of brain injury are now being recognized [3]. Clearly, additional research is needed to better understand the mechanisms of progressive brain injury that occurs during otherwise effective antiretroviral therapy.

One mechanism may be incomplete suppression of HIV replication in the brain by currently available antiretroviral regimens. Such regimens may be incompletely effective because the most potent drug of many regimens, the protease inhibitor, is extensively bound to plasma proteins, leaving little to penetrate into brain tissue. While several studies have confirmed low or undetectable concentrations of early protease inhibitors in cerebrospinal fluid (CSF) [4-6], the design of future studies is hampered by several logistical challenges. These challenges include 1) the suboptimal

pharmacokinetics of most protease inhibitors, 2) the need to per-

least 2 other drugs.

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.

form multiple lumbar punctures in an individual during a relatively brief period of time, and 3) the standard practice of simultaneously initiating protease inhibitors with at

A new AVRC-based study addresses these logistical challenges for the most recently approved protease inhibitor, Kaletra. First, the pharmacokinetics of the active drug, lopinavir, are markedly enhanced by its formulation with sub-therapeutic doses of ritonavir, an inhibitor of several cytochrome P450 isozymes. Such enhancement can result in higher protease inhibitor concentrations in CSF [7]. Second, rather than intensively sampling a small number of individuals, the study sparsely samples a larger number of individuals. This approach estimates population pharmacokinetics while reducing the number of lumbar punctures required per individual. Third, the study sequentially intro-

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AVRC Updates

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Kaletra in Cerebrospinal Fluid

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duces antiretrovirals to estimate Kaletra's independent effect on HIV replication in CSF. In Abbott 720, sequential introduction of Kaletra followed by d4T-3TC performed as well as simultaneous introduction of all drugs after 48 [8], 72, and 144 weeks. Importantly, no one in the sequential therapy arm developed resistance to Kaletra, even after 144 weeks of follow-up. By combining these 3 approaches, the CSF Kaletra Study aims to define the pharmacokinetics of lopinavir in CSF and to provide new insights into the effectiveness of protease inhibitors in the central nervous system.

Sixteen participants will be enrolled in this 24-week, open-label, single arm study of sequential introduction of antiretrovirals (Kaletra first, followed 3 weeks later by 2 nucleoside reverse transcriptase inhibitors). Eligible participants should meet guidelines for initiating therapy and be antiretroviral naive. Benefits of participation include a free phenotype assay, provision of Kaletra for the duration of the study, measurement of HIV RNA in plasma and CSF, reimbursement for lumbar punctures, and neuropsychological

testing (if subjects have symptoms of cognitive impairment). Participants must provide the non-Kaletra drugs in their regimen, in consultation with their primary medical provider. Laboratory results, including the PhenoSense GT assay, will be forwarded to providers, with participant permission. For questions or referrals, please call Scott Holder at the HNRC at 619-543-5020 or Dr. Scott Letendre at 619-543-4730.

1. Sacktor et al. *Neurology* 2001. 56:257-60
2. Masliah et al. *AIDS* 2000. 14: 69-74
3. Langford et al. *AIDS* 2002. 16:1019-29
4. Letendre et al. *Antimicrob Agents Chemother* 1998. 44: 2173-5
5. Moyle et al. *Clin Infect Dis* 1999. 28: 403-4
6. Aweeka et al. *JAIDS* 1999. 20: 39-43
7. van Praag et al. *AIDS* 2000. 14: 1187-97
8. Murphy et al. *AIDS* 2001. 15: 1-9

Two Research Studies of Abdominal Fat Treatment

1. Metformin

vs

Rosiglitazone

vs.

Both

(A5082)

2. 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.

The AVRC would like to thank the following:

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