
◆ Treatment Center News ◆

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STOPPING PCP PROPHYLAXIS

HOW DOES STOPPING PCP PROPHYLAXIS COMPARE TO STOPPING THERAPIES FOR OTHER OPPORTUNISTIC INFECTIONS? by Francesca Torriani, M.D.

Pneumocystis carinii pneumonia (PCP) remains the most frequent AIDS defining diagnosis even in the era of potent antiretroviral therapy. As with many other opportunistic infections, the risk of PCP is inversely correlated to the CD4 count and is highest once CD4 counts drop below 200 cells/mm³. In fact, only 5% of cases occur at higher CD4 counts. Because of the serious complications related to this infection, such as respiratory failure requiring admission to a specialized unit or even mechanical respiratory assistance in an intensive care unit, PCP is viewed as one of the most dangerous infections.

Since 1992, prophylaxis for PCP and prevention of recurrent disease is recommended in HIV patients with CD4 counts below 200. Trimethoprim/sulfamethoxazole (Bactrim, Septra) is considered the agent of choice because of its high efficacy in preventing PCP and other diseases such as toxoplasmosis, nocardiosis or other bacterial infections, low cost and relatively good tolerability. However, side effects are observed in about one third of patients, who will experience anything from fever, rash, diarrhea to liver toxicity. Other agents used are dapsone, aerosolized pentamidine, and atovaquone. These alternative regimens are substantially more expensive.

Unlike MAC or CMV disease, where inflammation plays

a very small role in the severity of the disease, severe PCP is associated with a spectacular inflammatory reaction in the lungs, causing massive leakage in the respiratory spaces followed by respiratory failure. Corticosteroids (prednisone) block this inflammatory response and have been shown to decrease the inflammation, reduce this early complication of PCP and result in an overall better outcome.

Since the use of protease-inhibitor containing regimens, the rate of PCP has dramatically diminished in patients taking PCP prophylaxis. In a French study presented last year, PCP events decreased by 60% in 1997 compared to 1996. In another study, ACTG 320, only 6 of 577 patients on the indinavir containing arm developed PCP, mostly in the first 3 months after starting antiretrovirals. In addition, there were no cases of PCP in patients with CD4 counts above 140 cells/mm³, indicating that the CD4 threshold for being at risk for PCP had not changed.

In recent years there has been increasing evidence that the rises in CD4 counts following potent antiretroviral therapy are associated with renewed protection against infections. In other words, the immune system is undergoing reconstitution. These effects have been observed even in patients without adequate suppression of HIV replication. Some scientists speculate that this protection afforded by the CD4 rise is only possible if the opportunistic agent is sufficiently common or present in high quantities in the environment. We think this is true for *Mycobacterium avium* complex, *Candida*, cryptococcus, as well as diseases that are acquired well before HIV infection and that re-activate, such as *Herpes simplex* and *Cytomegalovirus*.

Because PCP is present in the environment, patients who are responding to potent antiretroviral therapy, should be exposed to *Pneumocystis* and may acquire protection against new or recurrent disease. If this protection is granted by the renewed immune system, then stopping prophylaxis seems a reasonable option to allow patients to concentrate on taking their antiretroviral treatment.

This step should only be done in the setting of a clinical trial for the moment, to ensure adequate protection to patients,

see Stopping PCP Prophylaxis on page 7

NEW STUDIES ON STOPPING MAINTENANCE AND PROPHYLAXIS FOR PCP, CMV and MAC

- ◆ Stop PCP prophylaxis study (ACTG 888)
CD4 count > 200; history of PCP
- ◆ Stop CMV maintenance study (ACTG 379)
CD4 count >100 or 50-100 with decreased HIV RNA
- ◆ Stop MAC prophylaxis study (ACTG 362)
CD4 count > 100
- ◆ Stop MAC maintenance study (ACTG 393)
CD4 count >100

**for more information
call the Screening Coordinator
at 619-543-8080**

HIV RESISTANCE: CAN WE USE PHENOTYPE ASSAYS TO IMPROVE MANAGEMENT OF THERAPY?

by *Richard Haubrich, M.D.*

Although many options are available for antiretroviral (ARV) therapy, the reality of successful therapy, defined by HIV RNA below the limits of detection, has been seen less often in practice than with controlled clinical trials. In data from CCTG 570, a trial of HIV RNA monitoring, patients received unrestricted ARV therapy from their primary providers. The proportion who achieved and maintained HIV RNA < 400 was only 50%, well below the usual 80-90% seen in trials. A number of factors probably accounted for this sub-optimal result including: 1. adherence to therapy, 2. baseline viral load, 3. CD4 count, 4. use of prior therapy, and 5. viral resistance. The importance and interaction of these factors is not known. Attempts to address the first 3 factors are underway including use of adherence counseling, patient education and early ARV regimen intensification for patients with high viral loads who fail to reach undetectable levels. Prior exposure to ARV, especially as part of non-suppressive regimens, can lead to increasing resistance not only to the agents in the current regimen but also cross resistance to drugs in the same class.

HIV resistance arises from mutations in the viral genome to the proteins where the ARV drugs act. Changes to the pre-therapy genomic sequences (wild type virus) produce a new population of mutant viral particles. Mutations, arising during ARV therapy, may give the mutant virus a selective advantage and a new population of virus will emerge which is less sensitive to the drugs in the regimen. In addition, the accumulation of mutations can lead to cross-resistance to other agents in the same class of ARV.

Resistance has been characterized by genotype and phenotype assays. Genotype refers to the sequence of base pairs in the viral genome usually occurring in the reverse transcriptase (RT) and protease regions. A number of techniques are available to determine the genotype, some methods determine the entire RT and protease sequence while others only identify those sites associated with resistance. Differences in technique and questionable laboratory data have made choosing a genotype test difficult. The interpretation of the data is complex; although some clear associations between genotype and resistance are available (i.e., changes at position 184 and 3TC resistance), the correlation between genotype changes at other positions and resistance is less clear. The ability to account for the aggregate effect of multiple and disparate mutations which occur in different patients is even more complex although attempts to design computer software to interpret the data is an active area of research.

The resistance phenotype is the sum of the biologic effect of the genotypic changes. This allows the virus to multiply in the presence of drugs. Until recently, determination of HIV phenotypic resistance was complex, costly and slow. More

recent technologic developments have allowed rapid determination of phenotype (14 day assays) using plasma samples. Assays, such as one produced by ViroLogic, first amplifies, with polymerase chain reaction (PCR), patient derived viral sequences corresponding to the protease and reverse transcriptase encoded regions of the HIV genome. The patient derived segment is inserted into a viral test vector. The test vector contains the RT and protease genes from the patient and is transformed into viral particles that can to grow in cultured cells. These viral particles are then used to infect target cells. Protease inhibitors are added shortly after production, while reverse transcriptase inhibitors are added at the time of infection. The growth of these particles is measured and is a reflection of the ability of the patient's virus to grow in the presence of ARV drugs. The concentration of drug which inhibits 50% of viral replication is the IC₅₀ for that drug. The patient's IC₅₀ is divided by the control IC₅₀ to yield the fold resistance. If the fold resistance is greater than 1.0, then the patient's virus is less sensitive to the drug than control strains.

The role of resistance assays in clinical practice has yet to be determined. Many facets of the test need to be validated including accuracy, reproducibility, predictive value of the test and the impact of the results on clinical decision making. Initial data on the ViroLogic assay suggests that accuracy and reproducibility are good. In one clinical trial by Deeks, patients switching to a salvage regimen were more likely to have a prolonged virologic

see *Phenotype Testing on page 7*

Treatment Center News

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MOTHER AND CHILD TREATMENT EDUCATION

An Interview with Heidi Aiem - Health Educator

by Susan Okuno, L.C.S.W

The UCSD Mother, Child, Adolescent HIV Program has recently hired Heidi Aiem to provide health education to women, pregnant women, children and youth. Heidi has extensive experience working with women and children. Prior to joining UCSD, she worked for ten years in OB/GYN, most recently at Athena Women's Health/Birthplace. Susan Okuno, the program social worker, met with Heidi for a discussion of the challenges in providing health education to women and families living with HIV.

Heidi, please tell us how you became interested in working with this program?

"I've always been interested in working in the HIV field; I worked with HIV clients when I was an HIV pre and post test counselor at the Beach Area Community Clinic in 1988. I was inspired by Dr. Chaisson and others who work in the HIV field because of their energy and commitment to providing patient centered care and emphasizing the importance of health education. For the past ten years, I provided basic HIV education, counseling and testing to women in an obstetric and gynecologic practice. The practice I worked for felt very strongly about offering HIV counseling and testing to all of the patients. We referred all of the patients who tested HIV positive to the Mother/Child program and I thought it would be interesting and professionally challenging to work with the team here."

Let's talk for a moment about adherence. What do you see as the major challenges for women and children in adhering to their medical regimens?

"Probably the biggest challenge is that women have a tendency to take care of their partners' and childrens' needs

before their own. The reality is that its hard to take care of your own needs when you're taking care of someone else's. Life is complicated enough and then HIV throws in the need for multiple medical appointments, medications that can have difficult dosing schedules and unpleasant side effects and often, more frequent illnesses. Taking medication also requires that you accept your HIV diagnosis, and believe in and are committed to taking your medications every day."

What are the challenges for children living with HIV?

"Children face many challenges with HIV infection. Again, we're talking about lots of medical visits, medication and side effects and the daily grind of school and growing up. Many of the children in our program don't fully understand what is happening to their bodies and feel 'different' from their peers. They frequently take medications that taste terrible and have dosing schedules which interrupt their meals and daily activities. In addition, children are much more reliant on their parents and other family members for practical and emotional support. When it comes to medications, some children get excellent support and for some, the support just isn't there. For some families the medication schedule and the effort required to give medications present real problems."

How will you address these issues?

"Our program is very family-centered. We make a real effort to listen to our families and address their specific needs and concerns. We use what we hear from the family to tailor our educational services to meet their needs. We provide a supportive environment and use educational materials that are easy to understand and that aren't intimidating. Since everyone learns differently, we use some educational tools that are visually stimulating to enhance the learning experience.

It's very important to be accessible to families and to help them understand that we are here for them. I always encourage clients to ask questions and emphasize to them that no question regarding their health is a stupid question. I also encourage clients to learn as much as possible about their health condition so that they are better able to understand treatment recommendations and can be active participants, advocates if you will, in their own care."

For more information about the UCSD Mother, Child, Adolescent HIV program, please contact Mary Caffery at (619) 543-8080.

A Comparison Study of Protease Inhibitors and NNRTIs using NRTIs + efavirenz and/or nelfinavir (ACTG 384)

- ◆ Patients must have HIV RNA > 500
- ◆ Patients must not have had any prior PI, NNRTI, or 3TC use.

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

ADULT OPEN STUDIES

(revised 1/1/99)

for information about any of these trials, call 619-543-8080

Antiretroviral Studies

Study	Study Number	Study Design	Inclusion Criteria
ddI + d4T or AZT/3TC (Combivir) + Efavirenz OR Nelfinavir OR both	ACTG 384	Protease Inhibitor and/or NNRTI, comparison study	HIV RNA >500, no prior PI, NNRTI, or 3TC use.
Indinavir, Combivir, Nevirapine + IL-12 OR GM-CSF OR neither	ACTG 387	Immune System Stimulation	Treatment naive. HIV RNA > 20,000, CD4 > 300
Treatment + Adherence study All participants receive ddI + d4T + Efavirenz + Nelfinavir	AEH 003	Maximally assisted therapy (direct observation) vs. Self-administered therapy	Treatment Naive. CD4 > 200.

Treatment Intensification Studies

Indinavir + ddI + d4T vs. Indinavir + ddI + d4T + hydroxyurea vs. Indinavir + AZT(or d4T) + 3TC	ACTG 5025	Treatment Enhancement with hydroxyurea	HIV RNA < 200. Currently on IDV, AZT (or d4T) and 3TC > 6 months.
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Stop OI Prophylaxis or Maintenance Studies

OI Studied	Study	Study Number	Study Design	Inclusion Criteria
MAC	MAC prophylaxis discontinuation	ACTG 362	Continued vs. Stop Azithromycin	CD4 > 100 with history of CD4 < 50, No history of MAC dx
MAC	MAC therapy discontinuation	ACTG 393	Stop MAC maintenance	CD4 > 100; current HAART treatment
CMV	CMV Maintenance therapy discontinuation	ACTG 379	CMV Maintenance vs. no CMV Maintenance	Current HAART treatment, CD4 > 50, healed, non-active CMV
PCP	PCP prophylaxis discontinuation	ACTG 888	Stop PCP prophylaxis	CD4 > 200; history of PCP

Malignancy Studies (contact Dr. Saville - 543-2214)

Non-Hodgkins Lymphoma	Low dose Interleukin 2 or Interleukin 12		Stop PCP prophylaxis	CD4 > 200; history of PCP
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Other Studies

CMV	Roche Prodrug vs IV ganciclovir	RS 70070	Treatment of CMV Retinitis	New CMV retinitis, no prior CMV treatments, no systemic CMV
THRUSH	Fluconazole	ACTG 323	Prophylaxis vs Acute Therapy Study	At least 1 episode of thrush within last 24 mo.'s, not currently on thrush prophylaxis, CD4 < 150
MAC	MAC Immune Response Evaluation	ACTG 341	Various arms including Treatment or no Treatment	Contact Screening Person for this information
Acute/Primary HIV Infection Studies		AEH 003	Treatment plus adherence	Acute seroconversion or newly HIV+ with previous negative HIV test within last year. Treatment Naive.
		ACTG 371	Treatment study	

**PEDIATRIC AND PERINATAL
OPEN STUDIES** (revised 1/1/99)
for information about any of these trials, call 619-543-8080

Pediatric Studies

<u>Protocol</u>	<u>Drugs Being Studied</u>	<u>Study Design</u>	<u>Inclusion Criteria</u>
PACTG 366	Ritonavir, Nevirapine, Nelfinavir, ZDV, 3TC, d4T, ddI, ddC	Phase I/II study to compare combination treatment on HIV RNA. Open label, randomized according to previous drug history.	6 mo.'s - 21 yrs, disease progression or advanced disease while receiving treatment
PACTG 382	Liquid DMP-266, Nelfinavir plus one or more NNRTIs	Phase I/II study of pharmacokinetic safety, tolerance and anti-viral activity. Open label.	Ages 2 - 8 years old, naive to NNRTIs and protease inhibitors.
PACTG 397	TID Saquinavir (Soft Gel Cap) with two NRTIs vs. BID Saquinavir SGC +	Phase II study to assess the safety, tolerance and anti-viral effect of single and combination protease	3-16 years of age, able to swallow capsules, HIV RNA > 10,000, naive to one of the NRTIs in the study.

Perinatal Studies

ACTG 358	Maternal Indinavir, 3TC, ZDV; Infant 3TC & ZDV	Phase I trial of safety & efficacy and anti-viral activity during pregnancy & labor, & infant from birth to 6 weeks of age.	24-28 weeks gestation, normal pregnancy, normal ultrasound, no previous protease inhibitor use.
ACTG 316	Nevirapine vs placebo	Single dose of drug during labor and to the infant at birth	≥ 28 weeks gestation, may take any other antiretroviral therapy.
ACTG 331	ZDV in premature infants	Safety, tolerance and PK study in HIV exposed premature infants	HIV exposed, ≤ 34 weeks gestation, 1-5 days of age
ACTG 326	ALVAC HIV Vaccine alone or with Subunit Vaccine	Phase I/II study to evaluate safety, tolerance and immunogenicity of high dose vs. low dose vaccine vs. placebo on infant immune systems.	HIV+ pregnant women ≥ 37 weeks gestation are enrolled for care of their infant.
ACTG 367	Obstetric Chart Review	Review of obstetric and infant chart for usage of antiretroviral treatment.	All pregnant women who receive care or consultation at UCSD.

Other Studies

ACTG 254	Atovaquone & Azithromycin versus TMP/SMX	Phase II/III double-blind study of PCP prevention medications.	3 months - 19 years, Must require PCP prophylaxis
ACTG 219	No medications	Yearly visits including physical exams & neuropsychological testing of HIV+ and HIV exposed children	Infants & children who have been or are currently involved in any ACTG treatment studies
ACTG 247	24 calorie vs 20 calorie infant formula	Double-blind trial of 24 or 20 calorie formulas for at least 8 weeks in HIV exposed infants	HIV exposed infants, birth weight ≥ 1.8 kg, able to start formula by day 14 of age

HIV RELATED DEMENTIA

by *Scott Letendre, M.D.*

HIV enters the brain shortly after infection and can result in a spectrum of cognitive problems, from mild memory difficulties to severe dementia. Thirty to forty percent of HIV-infected persons with CD4 counts under 500 may develop mild forms of cognitive impairment, including difficulty with memory, reading, or taking medications. The Center for Disease Control estimates that 7% of persons with AIDS will develop HIV-associated dementia (HAD). We have found elevated levels of HIV RNA ("viral load") in spinal fluid of patients with dementia and milder forms of cognitive impairment. Antiretroviral drugs have clinical benefit in some patients with HAD. This benefit is thought to be partially due to their ability to penetrate into the brain and spinal fluid and reduce viral load. Some reverse transcriptase inhibitors, such as AZT, d4T and nevirapine, penetrate into the brain and spinal fluid well. Other drugs, most notably the protease inhibitors, are bound to proteins in the blood and may not penetrate well enough to suppress HIV replication in the brain.

The Cognitive Intervention Trial at the HNRC asks the questions: 1) Is spinal fluid viral load a useful tool for monitoring patients? and 2) Do combination antiretroviral regimens reduce blood and spinal fluid viral load and protect or improve cognitive function? Participants in this trial obtain their antiretroviral medications from another study or their own provider but receive free laboratory tests and payments for spinal taps. After enrollment, they are seen approximately every 4 weeks and evaluated with blood, spinal fluid, and neuropsychological tests. Between the baseline and week 12 visits, the first 16 participants showed at least a 1 log decrease in viral load in both blood and spinal fluid. Patients who had a reduction in spinal fluid viral load improved their cognitive function. Those who reduced the viral load in blood alone did not. Therefore, spinal fluid viral load may be an important clinical tool for monitoring the neurologic manifestations of HIV.

A patient who is having new memory problems, difficulties with understanding instructions or reading, should call the HNRC for a telephone screening with Teresa Oyo at (619) 543-5045.

HYDROXYUREA STUDY (ACTG 5025)

Indinavir + ddI + d4T

vs.

Indinavir + ddI + d4T + hydroxyurea

vs.

Indinavir + AZT (or d4T) + 3TC

Inclusion criteria:

- must have undetectable HIV RNA
- currently be taking indinavir, 3TC, and AZT (or d4T).

Call (619) 543-8080.

Ask for the Screening Coordinator

CPI 1189 IN HIV ASSOCIATED COGNITIVE IMPAIRMENT

by *Ron Ellis, M.D.*

The "CPI trial" will enroll individuals with established HIV infection who are experiencing difficulties with concentration, attention and thinking abilities. Most of these individuals will also be taking antiretroviral combination therapies. CPI-1189 is an experimental drug that acts as an antioxidant and also inhibits some of the chemical changes that result from abnormal immune system function. The study is 2-arm placebo controlled study. As part of the screening phase for this study, volunteers will undergo a physical examination, laboratory tests, and paper-and-pencil tests of memory, attention and thinking (cognitive tests) to determine if they are eligible for enrollment. If enrolled, a lumbar puncture will be performed, and follow-up study visits are required at baseline and at weeks 2, 6 and 10. The laboratory tests and cognitive tests will be repeated at week 10. Volunteers may also participate in an optional, 10-week, "open label" extension phase in which all participants will receive active study drug, CPI-1189.

This study is sponsored by the Neurologic AIDS Research Consortium (NARC) of the AIDS Clinical Trials Group (ACTG). For more information, call Teresa Oyo

UCSD Treatment Center Mission Statement

The mission of the UCSD Treatment Center is to develop and perform high quality research protocols which enhance the treatment of HIV-related illnesses while respecting and supporting the best interests of our clients. We will maintain a safe and caring environment for our clients and our staff.

PHENOTYPE TESTING

continued from page 2

response if they had 2 or more drugs in the new regimen to which the virus was susceptible as opposed to those patients whose virus was susceptible to one or none of the drugs in the regimen.

Whether or not phenotypic resistance assays can improve the clinical decision process of selecting a new ARV regimen over that based on ARV history, CD4 cell count and viral load is pressing question. Introduction of new testing procedures for HIV infected patients needs to be carefully investigated since assays, such as those evaluating HIV phenotype or genotype resistance, are expensive, may require 2-4 weeks for results and may not improve overall management. Introduction of a new assay should ultimately result in improved HIV RNA suppression and improved clinical outcome. A clinical strategy study is the ideal method to help define the utility of a new HIV testing procedure.

CCTG 575 is a multicenter, randomized, comparative study of two clinical management strategies for optimizing antiretroviral (ARV) therapy in HIV-infected patients with plasma viral load measurements >400 copies/mL; use of a new HIV phenotypic drug susceptibility assay plus conventional therapy guidance criteria (HIV RNA levels, CD4 cell counts, and clinical parameters) versus use of conventional criteria alone. Viral load and CD4 will be measured every 2 months in both groups; the phenotype strategy group will have the phenotype assay done whenever the viral load is > 400 copies/mL. The primary outcome of the study is the overall suppression of HIV RNA achieved over the 12-month follow-up period (using an area based measure).

This important clinical trial has started at the Owen Clinic and VA Medical Center. Accrual will continue for 6 months and follow-up for 12 months after the last patient is randomized. We look forward to continued updates from this important study. Please call the Treatment Center at (619) 543-8080 for referrals or for more information.

STOP PCP PROPHYLAXIS

continued from page 1

ideal monitoring of recurrence and unusual presentations or complications of this infection.

ACTG 888 is designed to study the safety of discontinuing PCP prophylaxis in 250 patients with or without prior PCP and an increase in CD4 counts above 200 cells/mm³ in response to potent antiretroviral therapy. The study is still actively accruing patients with a history of prior PCP. Patients will be asked to stop their PCP prophylaxis and will be evaluated for symptoms and CD4 counts every 2 months until the end of the study. Blood for HIV viral load and for future immunology will be stored every 4 months. This trial is expected to last 3 years at most. PCP prophylaxis will be resumed if CD4 counts drop below 200 cells/mm³. At UCSD, 20 of a projected 50 patients have already been enrolled since October 98. Patients will be offered \$20/visit to cover transportation costs.

This study will allow us to identify which patients should stop PCP prophylaxis and what are the consequences of such an intervention in a very safe and objective manner. Because collaboration between the UCSD Treatment Center staff, the patients and their providers is very close in San Diego, I have no doubt that this trial will enroll enthusiastically. Please do not hesitate calling the UCSD Treatment Center, at (619) 543-8080, for referrals or for more information.

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