

EARLY HIV TREATMENT AND LATENTLY INFECTED T-LYMPHOCYTE RESERVOIRS

by Joe Wong, MD and Susan Little, MD

Despite the significant benefits of newer combination antiviral treatment for patients with established HIV-1 infection, existing therapies fall short of eradicating infection. One recently recognized obstacle to viral eradication in patients receiving potent antiretroviral therapy is the persistence of a reservoir of latently infected lymphocytes despite years of apparently effective suppression of HIV replication [1]. Thus, in studies done primarily in patients with chronic HIV infection, cells carrying replication competent virus have been recovered up to 2.5 years after persistent suppression of plasma RNA to undetectable levels [2-4]. In fact, the average half-life of this latent reservoir has been estimated at 44 months [5]. Thus in patients with established infection, the likelihood of eradication of infection appears remote with existing therapies.

There is interest and hope however, that the challenge of viral eradication with existing potent therapies may be more feasible in subjects who initiate antiretroviral therapy within weeks or months of initial HIV infection. It has been proposed that a more effective HIV-specific CD4 cell response is preserved when treatment is initiated very early following infection. In theory this could lead to more effective immune surveillance and clearance of both productively infected cells and latently infected cells as they are activated in vivo. Supporting this latter possibility is the observation that, although latently infected cells can be demonstrated soon after primary infection [6], the decay rate of latently infected cells in patients with primary HIV infection (ie, less than 12 months after HIV infection) who initiate potent therapy has been estimated at approximately 6 months. This faster decay rate would shorten the proposed duration of completely suppressive therapy necessary to achieve viral eradication in 7 to 10 years [7]. Notably, the subjects in this study were not all "acutely infected" when they began treatment and it is possible that treatment initiated at an even earlier time after HIV infection

could result in more rapid decay of this reservoir. Existing studies have had insufficient numbers of such patients to accurately answer these questions.

Investigators at the UCSD Treatment Center and laboratories, are interested in evaluating the potential for viral eradication in the setting of primary HIV infection. Funded by grants from the State of California and the National Institutes of Health, we have established a regional network to identify and recruit patients newly infected with HIV with a particular emphasis on those individuals presenting with a history of recent exposure and "flu-like" symptoms of the acute retroviral syndrome. These efforts have already resulted in several important observations about viral dynamics during the acute infection period [8] and the epidemiology of transmission of HIV with reduced susceptibility to antivirals [9]. In collaboration with colleagues across the state, we hope to recruit sufficient numbers of patients at the very earliest periods following HIV infection to address the issue of the clearance of the reservoir of latently infected cells in patients receiving potent combination antiviral therapy.

We welcome referrals of patients with documented infection of less than 1 years duration. Patients with a compatible history of recent infection, but without prior HIV antibody and y test results will be screened using a "detuned" HIV antibody test [10]. This modified HIV EIA will provide an estimated duration of HIV infection in subjects infected within the previous 6 months. Subjects who are referred with symptoms of an acute retroviral illness will be screened by plasma HIV RNA detection. All patients with serologic and virologic test results to suggest HIV infection within the last 90 days will be eligible for study participation. Eligible subjects will have the option of screening for co-enrollment to one of several potent combination antiretroviral treatment studies offered

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Mission Statement

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.

Results from the First Randomized Study of Salvage Therapy: ACTG 359

by *Richard Haubrich, MD*

The past several years have seen great progress in the treatment of HIV infection with antiretroviral therapy. Although HIV protease inhibitors have dramatically reduced clinical progression and death in HIV infected patients, success of therapy, defined as a HIV RNA < 400 copies/ml is not always achieved. In CCTG 570, one study where patients were treated with a variety of HAART regimens, only 40% of patients maintained viral loads less than 400 after 6 months. Thus, there is an increasing number of patients who fail the initial treatment regimen and the optimal treatment for these patients is not clear.

ACTG 359 was one of the first prospective, randomized, partially-blinded studies designed to address several questions regarding salvage therapy. First, what is the overall success rate of a salvage regimen in patients who had failed one prior protease inhibitor (indinavir). Second, what are the components of the salvage regimen that contribute to success of therapy and finally which baseline factors, such as CD4 cell count, viral load and HIV resistance, effect the success of therapy. Patients were enrolled if they had received indinavir for at least six months, had never received a non-nucleoside reverse transcriptase inhibitor and had HIV RNA levels of 2000-200,000 copies/ml. Overall, 277 patients participated in the study; 13 were seen at the Treatment Center.

All patients received a 3 or 4 drug regimen consisting of 2 protease inhibitors plus 1 or 2 other drugs. There were 6 total groups.

Three groups received:

ritonavir + saquinavir plus:
delavirdine or
adefovir or
delavirdine + adefovir.

The other three groups received:

nelfinavir + saquinavir plus:
delavirdine or
adefovir or
delavirdine + adefovir.

Subjects were assessed for safety and tolerability of the study medications and changes in virologic and immunologic parameters for 24 weeks. The primary analysis of this trial examined the proportion of patients who had viral loads below 500 copies 16 weeks after starting study medication.

The median length of prior indinavir use for patients in the study was 14 months, median baseline HIV RNA was 31,746 (4.5 log₁₀) copies/ml and CD4 cell count was 229 cells/mm³. Five percent of subjects had viral load levels <2,000 copies/ml at study entry, 36% had levels 2,000 to 20,000 copies/ml, and 58% had levels >20,000 copies/ml. The six treatment groups had similar baseline characteristics.

Overall, by week 16 only 30% of subjects had HIV RNA levels ≤500 copies/ml. One of the primary goals for the study

was to determine which dual protease inhibitor regimen produced the greatest viral load response. A comparison of ritonavir/saquinavir failed to show any difference compared to nelfinavir/saquinavir (28% vs. 33%, p=0.50). Thus, choice of ritonavir or nelfinavir for the second PI with saquinavir in a salvage regimen did not appear to effect the outcome. However, there was a difference with the use of delavirdine for the nucleoside/non-nucleoside portion of the regimen. Patients who received delavirdine had a better virologic response (40% vs. 18%, p=0.002) than those who received adefovir. Adding adefovir to delavirdine did not improve the response over delavirdine alone (40% vs. 33%, p=0.42).

Advanced statistical techniques were used to examine the effects of baseline factors on virologic response. The following were found to increase the likelihood of having a viral load < 500 copies/mL at week 16: higher baseline CD4 cell counts, lower baseline HIV RNA levels, shorter duration of prior indinavir use and female gender. After accounting for these factors, delavirdine continued to have a significantly greater virologic response rate than adefovir.

CD₄ cell counts increased an average of 19 cells/mm³ from baseline and there was no significant difference in CD4 cell increases in any of the treatment groups. There were no significant associations between baseline factors and change in CD4 cell count.

Since mild symptoms were not recorded in this trial, the majority of all signs and symptoms were moderate in intensity. The most common of these were diarrhea (26%), pain

see *Salvage Therapy on page 7*



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Consequences of Limited Penetration of Protease Inhibitors into the Brain

by Scott Letendre, MD - HIV Neurobehavioral Research Center

Multiple anatomic safeguards protect the brain, including a complex barrier that limits the penetration of dangerous chemicals and microorganisms, even as it allows passage of important nutrients. Despite this barrier, HIV is able to penetrate into the brain and establish chronic infection. In some people, HIV brain infection manifests as problems with memory and thinking.

When used in combination with other medications, protease inhibitors may dramatically reduce HIV levels in the blood, preserve immune function, and prolong the survival of people living with HIV. Despite their many benefits, these drugs may not penetrate into the brain and spinal fluid because they are highly bound to proteins in the blood. In fact, in most patients, protease inhibitor therapy alone does not reduce HIV levels in the spinal fluid, and presumably the brain, below detectable. Fortunately, combining protease inhibitors with other anti-HIV drugs often does. This is illustrated by the following research findings:

Individually, zidovudine (AZT) and didanosine (ddI) (Fortovase) penetrate poorly into the spinal fluid. When used together, zidovudine boosts didanosine levels in the blood. Despite this boosting effect, the combination still does not suppress HIV in the spinal fluid in all patients. However, people who added ddC (Zerit) to these protease inhibitors were 30 times more likely to suppress spinal fluid HIV levels below detectable after 12 weeks of therapy.

Nelfinavir (Viracept) was completely undetectable in the spinal fluid of six patients, despite therapeutic blood levels. However, since nelfinavir was combined with other anti-HIV

drugs in this study, most of the patients still reduced the amount of HIV in their spinal fluid.

Indinavir (Crixivan) is bound to blood proteins less than the other protease inhibitors and so probably has the best brain penetration. In one study of indinavir combined with 2 other anti-HIV drugs, 90% of people had undetectable HIV levels in the spinal fluid.

Together, these studies support that combining protease inhibitors with other drugs reduces HIV levels in the spinal fluid. Unfortunately, this does not occur in all people. Such a lack of response may be due to drug resistant HIV, which may be found either in the blood, in the spinal fluid, or in both. When someone has sensitive HIV in the blood but resistant HIV in the spinal fluid, the reduced levels of protease inhibitors present in the spinal fluid are unable to suppress the resistant HIV, which may then migrate out of the spinal fluid and into the blood and lymph nodes. Once the resistant HIV enters the blood and lymph nodes, viral load increases and immune damage progresses.

In conclusion, combination therapy continues to hold great promise for controlling HIV infection. However, some people may not respond fully since HIV levels in spinal fluid may remain elevated even as blood levels are reduced. This situation may result in the development, and subsequent spread, of resistant HIV. At the HRNC, we are conducting studies to specifically study the penetration of antiretrovirals into the spinal fluid, the development of resistant HIV in spinal fluid, and the cognitive consequences of antiretroviral treatment. To learn more, please call Rodney von Jaeger (619)543-5055 or Scott Holder (619) 543-5020.

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.

Please call Scott Holder to find out more
(619) 543-5020

HIV Neurobehavioral Research Center
2760 Fifth Ave. Suite 200 San Diego, CA 92103

Research Study available to find the best way to prevent reoccurring

Thrush

(Oral Candidiasis) (ACTG 323)

to be eligible:

- ◆ **must have CD4 < 150**
- ◆ **must have had at least one episode of thrush within the past 24 months**
- ◆ **may not currently be using chronic suppressive therapy for thrush such as fluconazole.**

call the screening coordinator at 619-543-8080

ADULT OPEN STUDIES:

for more information on any of these trials, call (619) 543-8080

Antiretroviral Studies

Study	Study Number	Study Design	Inclusion Criteria
Indinavir Intensification study (<i>salvage</i>)	Abbot M-98-985	Treatment enhancement with Ritonavir	Currently on indinavir regimen. HIV RNA between 50 and 50,000.
ddI + d4T or AZT/3TC (Combivir) + Efavirenz OR Nelfinavir OR both (<i>initial</i>)	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 (<i>initial</i>)	ACTG 387	Immune System Stimulation	Treatment naive. HIV RNA > 20,000, CD4 > 300
Treatment + Adherence study. All participants receive: ddI + d4T + Efavirenz + Nelfinavir (<i>initial</i>)	AEH 003	Maximally assisted therapy (direct observation) vs. Self-administered therapy	Treatment naive. CD4 > 200.
DAPD (NRTI) (<i>phase 1</i>)	DAPD 101	Phase 1 study. 15 day study of DAPD only.	Prior AZT/3TC or D4T/3TC use. DDI and DDC naive. CD4>50. HIV RNA between 5000 and 250,000
Amprenavir, Abacavir, Efavirenz, Ritonavir + or - T-20. (<i>salvage</i>)	T20-206	Phase 2, dose-assessment study of T-20.	HIV RNA between 400 and 100,000. Past PI use. Naive to NNRTIs and Amprenavir, Abacavir, Efavirenz, and T-20.
BMS 232632 (Daily-dose PI) + DDI + D4T vs. Nelfinavir + DDI + D4T (<i>initial</i>)	BMS 007	Phase 2, nelfinavir vs. BMS: protease comparison study	Treatment naive. CD4 > 100. HIV RNA greater than 2000.

Opportunistic Infection and Stop O.I. Therapy Studies

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
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

Acute/Early Infection Studies

Acute/Early HIV Infection Pathogenesis and Latency study	AEH 005	Observational study of viral dynamics	Acute/Early HIV infection (less than 90 days)
Combivir (AZT/3TC) +amprenavir + abacavir	ACTG 371	Treatment during acute/early HIV infection.	Acute/Early HIV infection (less than 90 days)

Other Studies

Malignancy Studies: Kaposi Sarcoma and Non-hodgkins Lymphoma.	For information, call Dr. Saville - 543-2214		
Memantine	ACTG 301	AIDS Dementia Complex	Memory Problems. Current anti-retroviral therapy or off ARV therapy for 6 weeks.
Effects of switching from protease regimen to Efavirenz (NRTIs do not change) in patients with lipid distribution abnormalities.	CCTG 577	Immediate switch to Efavirenz vs. continue protease regimen for 6 months. All receive diet and exercise counseling.	HIV RNA < 50. Currently on PI + 2 NRTIs. NNRTI naive. Lipid distribution abnormalities or high lipids.

PEDIATRIC AND PERINATAL OPEN STUDIES

for more information on any of these trials, call (619) 543-8080

Pediatric Therapy Studies

Study Number	Study	Study Design	Inclusion Criteria
PACTG 345	Ritonavir, 3TC, AZT	Determine dosing , safety and efficacy	Ages 4 weeks - 2 years with specific CDC classifications
PACTG 366	Ritonavir, Nevirapine, Nelfinavir, ZDV, 3TC, d4T, ddI, ddC	Open label study to compare combination treatments	Ages 6 mo - 21 yrs, disease progression or advanced disease while on treatment
PACTG 381	HAART-at least 3 drugs including 1 PI	Study to define the immunologic reconstitution in recently infected adolescents	Ages \geq 8 - 22 yrs, treatment naive or monotherapy only, not infected at birth, detectable HIV RNA
PACTG 382	Liquid DMP-266, NFV plus 1 or more NNRTIs	Determine safety, and efficacy	Ages 2 - 8 yrs, naive to NNRTIs and PI's
PACTG 397	TID SQV _{sgc} with 2 NRTIs vs. BID SQV _{sgc} + NFV with 2 NRTIs	Assess safety and efficacy of single and combination protease therapy	Ages 3-16 yrs, able to swallow capsules, HIV RNA >10,000, naive to one of the NRTIs in the study
PACTG 403	ddI, Nelfinavir, Ritonavir vs. d4T, Nelfinavir, Nevirapine	Assess safety and efficacy of combination therapy	Ages 4 mos - 21 yrs, clinically stable, HIV RNA >4000, on same antiretrovirals for at least 16 wks.

Perinatal Studies

ACTG 316	Nevirapine vs placebo	Single dose of drug during labor and to the infant at birth	\geq 28 weeks gestation, may take any other antiretroviral therapy
ACTG 326	ALVAC HIV Vaccine alone or with Subunit Vaccine	Assess safety and efficacy vaccine vs. placebo on infant immune sys-	HIV+ pregnant women \geq 37 weeks gestation enrolled for care of infant
ACTG 331	ZDV in premature infants	Safety and efficacy in HIV exposed premature infants	HIV exposed infants, \leq 34 weeks gestation, 1-5 days of age
ACTG 358	Maternal Indinavir, 3TC, ZDV; Infant 3TC & ZDV	Assess safety & efficacy in pregnancy, labor, & infant from birth to 6 weeks	24-28 weeks gestation, normal pregnancy, normal ultrasound, no previous PI's

Other Studies

ACTG 219	No medications	Yearly visits inc. physical exams & neuropsychological testing of HIV+ and HIV exposed children	Infants & children who have been/are currently involved in any ACTG treatment studies
ACTG 247	24 vs 20 calorie per ounce infant formula	Assess growth in HIV exposed infants with 24 vs 20 calorie per ounce formula	HIV exposed infants, birth weight \geq 1.8 kg, able to start formula by day 14 of age
ACTG 247	24 vs 20 calorie per ounce infant formula	Assess growth in HIV exposed infants with 24 vs 20 calorie per ounce formula	HIV exposed infants, birth weight \geq 1.8 kg, able to start formula by day 14 of age
ACTG 254	Atovaquone & Azithromycin versus TMP/SMX	Assess efficacy of PCP prevention medications	Ages 3 months - 18 months, must require PCP prophylaxis
P1008	Discontinuation of PCP/MAC Prophylaxis	Assess rate of OI's in immunologically stable children	Ages 2 - 21 yrs, stable CD4% for at least 3 months must be willing to discontinue PCP and MAC prophylaxis.

NEW RESEARCH STUDY:

T-20

(FUSION INHIBITOR)

Study Design: Amprenavir, abacavir, efavirenz, ritonavir with or without T-20.

Inclusion criteria:

- HIV RNA between 400 and 100,000
- Past protease inhibitor use
- Never taken efavirenz, nevirapine, delavirdine, amprenavir, abacavir, or T-20.

Call the screening coordinator: 619-543-8080.

**Research Study: Switch Regimens
in those 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

**Research Studies available on
STOPPING MAINTENANCE
MEDICATIONS
for PCP, CMV and MAC**

Stop PCP maintenance study (ACTG 888)

*(*closing soon)*

CD4 count > 200; history of PCP

Stop CMV maintenance study (ACTG 379)

**CD4 count >100 or 50-100 with
decreased HIV RNA ; history of CMV**

Stop MAC maintenance study (ACTG 393)

CD4 count >100; history of MAC

**call the Screening Coordinator
at 619-543-8080**

E A R L Y H I V

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to subjects with primary HIV infection or may receive anti-retroviral therapy from their care provider. In addition, subjects who do not wish to initiate antiretroviral therapy will be eligible for study participation as part of natural history cohort. Studies to estimate the size and decay rate of the pool of latently infected cells in untreated patients will provide invaluable information in our attempts to determine these same parameters in subjects receiving therapy. Study subjects will have whole blood samples collected at regular intervals during study follow-up for isolation of a highly purified subset of CD4 cells. These cells will be analyzed in a quantitative, terminal dilution format for replication competent virus in tissue culture.

The successful completion of these studies should allow us to answer the following questions: 1. How large is the reservoir of latently infected cells in the acute and the early HIV infection stages? 2. What are the clearance rates of this reservoir in these two stages? 3. Based on the answers to 1 and 2, what are the estimates for time to eradication of infection if patients can be identified and treated early enough following acute infection?

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, and ask to speak with the screening coordinator for further information. Providers wishing to refer symptomatic high risk individuals for Acute HIV screening are encouraged to call Dr. Little at (619) 543-8080 (business hours) or (619) 543-6737 (study doctor on call after hours).

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Salvage Therapy

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(13%), nausea (12%), and fatigue (12%). Forty-eight (17%) subjects reported severe or greater signs and symptoms. There were not significant differences between the groups in the time to occurrence or rate of adverse events. Three (1%) subjects experienced PRTD over the first 16 weeks and all took adefovir-containing regimens. Further analysis of patients containing adefovir for longer periods of time are ongoing.

In summary, a third of subjects who experienced virologic failure on an indinavir-containing regimen suppressed viral load levels taking a new combination regimen of dual protease inhibitors, delavirdine and/or adefovir. Patients with lower baseline viral load, higher CD4 cell counts and shorter duration of prior indinavir tended to have more favorable responses. The presumed reason for greater success in patients with lower viral load and shorter duration of indinavir is lower levels of indinavir resistance and cross-resistance to other PI regimens. Preliminary data from CCTG 575 suggests that prior treatment with indinavir is more likely to produce cross-resistant virus than prior nelfinavir and that the duration of prior PI use increases the number of drugs with phenotypic resistance. Thus, the poor response to the ACTG 359 regimens may be due to highly cross-resistant viruses. New approaches that favor early treatment "intensification" and the introduction of new drug classes are needed. The Treatment Center will focus on such trials in the next several months.

A Community Update....

HIV Treatment in the New Millenium Update from the ICAAC conference

New Treatments
Metabolic Complications

Resistance
Opportunistic Infections

Speakers:

David Hardy, M.D. - Pacific Oaks Medical Group
Richard Haubrich, M.D. - The UCSD Treatment Center
Steve Oppenheim, M.D. - Robert Smith Medical Group
David Shamblaw, M.D. - Robert Smith Medical Group

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