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Progress and New Studies in Primary HIV Infection by Susan Little, MD

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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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The "First Choice Program"

The UCSD primary infection "First Choice Program" is an NIH-funded initiative focused on conducting studies that provide insight into the earliest events of HIV infection. These studies are relevant to our efforts to optimize treatment interventions and develop effective vaccines. In addition, the identification of newly infected subjects provides an opportunity to address HIV transmission, prevention and provide necessary HIV education to the newly infected study participant and their potential source partners. Since the initiation of our program in July 1996, the San Diego First Choice Program has evaluated 241 referrals for acute or early HIV screening of which 114 (47%) had well-documented primary HIV infection, 55% of whom were identified prior to the development of a mature HIV Western blot. Study results from our group and others have provided important insights that are affecting the management and treatment among these newly infected subjects.

Drug Resistance

The transmission of drug resistant virus to a newly infected individual has the potential to limit the response to immediate or delayed treatment and may permit selection for additional drug resistant variants in the setting of sub-optimal therapy. Our group leads a National collaborative effort to define the prevalence of transmitted drug resistance in recently infected subjects. Recent data from this group demonstrate that just over 20% of newly infected subjects (identified in 1999-2000) are infected with a virus resistant to one or more ARV drugs. These study participants did not receive prospective drug resistance testing; the choice of initial regimen was specified by study protocols or standard of care practices. Transmitted drug resistance was associated with a slower time to complete virologic suppression and a shorter time to virologic failure. These prevalence estimates suggest that treatment according to empirical guidelines may not be associated with sustained virological suppression in newly in-

fecting patients.

Treatment and Treatment Interruption

Our group is also conducting studies to understand more about the reservoir of HIV established at the earliest stages of disease. The establishment of a reservoir of latently infected CD4+ memory T cells during the first few weeks of HIV infection provides a mechanism for life-long persistence of infection, despite the use of potent and effective antiretroviral therapy. Furthermore, the persistence of a transmitted drug resistant variant within the latent reservoir enables the emergence of the resistant variant if the selective drug pressure of a particular drug is imposed. Although potent combination therapy is associated with sustained viral suppression in the majority of treatment-naïve subjects infected with drug susceptible virus, the half-life of the latently infected cell reservoir (43.9 months) suggests that viral eradication is not likely to be achieved using available therapies among patients with established infection. Preliminary observations from our group and others suggest that among patients initiating therapy during acute HIV infection, the rate of HIV decay within latently-infected cellular reservoirs may be more rapid than among patients initiating therapy during chronic HIV infection. Furthermore, complete virologic suppression may be more readily achieved among patients who start therapy during acute or early infection as compared to those who start therapy later in the course of their infection.

Therapeutic Immunization

The therapeutic immunization of HIV infected individuals represents a novel approach to augmenting HIV-specific immune responses. The UCSD Primary Infection Group is working with Merck in the development of a clinical trial to test an HIV vaccine construct (in an adenoviral vector) in patients with recent HIV infection. The importance of virus-specific immune responses has been clearly demonstrated for a

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Therapeutic Drug Monitoring (TDM):

Has the time arrived for routine clinical use?

by Richard Haubrich, MD

Although the success of antiretroviral therapy has greatly improved the survival of people living with HIV, some people do not achieve viral load levels below detection. Many causes have been proposed to explain why the treatments do not work for all patients. Many factors including individual differences in drug disposition (pharmacokinetics), adherence, prior therapy, CD4 count, HIV RNA, and phenotypic resistance interact to determine the response to antiretroviral (ARV) therapy. Among the many factors related to antiretroviral treatment failure, inadequate blood levels of the agents, particularly of the protease inhibitor, may be an important explanation. Several studies have demonstrated that patients failing to maintain HIV RNA suppression have lower levels of protease inhibitors than in those who achieve undetectable viral loads. In the pharmacokinetic study of ACTG 343, patients with HIV RNA < 200 copies/mL after 24 weeks of therapy with IDV + ZDV + 3TC had significantly higher IDV C_{min} concentrations (0.24 +/- 0.2 mg/mL) compared to patients failing the regimen with HIV RNA > 200 copies/mL (0.13 +/- 0.09 mg/mL, $p = 0.008$). In another study by Decamps¹, lower levels of IDV were also found to be an important predictor in patients with early virologic rebound.

The VIRADAPT² study, a clinical trial that was conducted in France provided information that sub-optimal protease inhibitor levels predicted virologic outcome even after considering the effect of genotype guidance of therapy. The primary study randomized patients to receive new regimens chosen on the basis of genotype versus standard of care. The main study demonstrated the benefit of resistance testing as patients in the genotype group had better viral load reduction than the no-genotype group. In a retrospective analysis, protease inhibitor levels were determined for 85 patients. Multiple levels were run for each patient. Patients

who had 2 or more protease inhibitor concentrations below the IC_{50} of the protease inhibitor they were receiving were considered to have sub-optimal concentrations. The reduction in HIV RNA from baseline was about 0.5 \log_{10} copies/mL less for patients with low drug concentrations compared to those with higher drug levels. Patients with low concentration had poorer virologic responses at week 48 in both the genotype and standard of care groups. In a multivariate model (a statistical technique that separates out the effect of one factor versus another), low PI concentrations were an independent predictor of change in viral load even after correcting for the effect of genotypic assisted therapy.

These studies suggest that individual patient differences in absorption, distribution and metabolism of the protease inhibitors results in different drug concentration profiles, which have an impact on response to ARV therapy. It is well known that differences between people, such as gender, age, weight, cytochrome enzyme function (a measure of the liver's ability to metabolize drugs), may lead to large differences in the concentration of protease inhibitors in the blood. The goal of the therapeutic drug monitoring (TDM) is to determine individual patient drug profiles, as estimated by measuring drug concentration in the blood, in order to achieve an optimal concentration of drug to suppress virus and avoid toxicity.

Several studies of antiretroviral therapy have demonstrated an effect of higher drug dose or drug concentration on the incidence of treatment related toxicity. One study of amprenavir (APV) evaluated three different doses (900, 1050, and 1200 mg given 3 times daily) with AZT plus 3TC³. In addition to demonstrating an effect of dose on virologic response, the study showed that higher doses were accompanied by increased toxicity. Drug-related rash was greater with higher APV doses. The

incidences was 5%, 15%, and 45% for 900, 1050, and 1200 mg APV doses, respectively ($p=0.003$ by posthoc comparison). The proportion of patients who discontinued APV due to the development of an adverse event was higher with increased APV dosing: 10%, 10%, and 40% for the 900, 1050, and 1200 mg groups, respectively ($p=0.022$ by posthoc comparison).

A relationship between indinavir (IDV) and toxicity has also been demonstrated. Burger⁴ evaluated 19 patients receiving IDV 800 mg every 8 hours with 8-hour pharmacokinetic curves at week 4 of therapy. The study defined nephrotoxicity as flank pain, hematuria, or an increase in serum creatinine of >25%. The concentrations of IDV were similar to previous studies and correlated with weight. Patients with elevated C_{max} (above 10 mg/L) and AUC (above 30 mg/L per h) had greater incidence of nephrotoxicity, but there was no association between C_{min} and nephrotoxicity.

Although it is clear that low PI and NNRTI concentrations predict reduced virologic success and that elevated concentrations increase the likelihood of toxicity, there are many questions that need be addressed before therapeutic drug monitoring can be incorporated into clinical practice. Among the issues that need to be considered are:

A. What are the clinical (CD4, HIV RNA, AIDS history) and genetic (P-glycoprotein and cytochrome P450 alleles) factors predictive of sub-optimal plasma concentrations?

B. Which method should be used to measure the level?

C. Which pharmacological parameter should be measured- C_{min} , C_{max} , AUC and how should these parameters be evaluated (i.e., single trough measure, sparse sample or full PK sampling)?

D. What is the cut point for considering a PI or NNRTI level to be

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Optimal Therapy during Pregnancy

New Perinatal Trials Study HIV Therapy During Pregnancy

by Mary Caffery, RN, MSN

The optimal therapy for HIV infection in pregnant women is not yet known. A series of new studies to examine efficacy and safety of treatment regimens have recently opened. The timing is important. Nationwide, one in five HIV infections occur among women, the majority of whom are in their childbearing years. The rates of HIV testing during prenatal care are improving leading to the increased identification of HIV positive pregnant women. Nearly one half of the HIV infected pregnant women in the U. S. receive their diagnosis during pregnancy. Even among women with an HIV diagnosis prior to pregnancy, antiretroviral therapy may not be initiated until pregnancy. In addition, many women with stable HIV infection are now choosing to have children.

Three new studies are now available

to examine the impact of HIV treatment during pregnancy:

[PACTG 1022: A Phase III, Open Label, Randomized Trial Of A Protease Inhibitor Including vs. A Protease Inhibitor Sparing Regimen for Initial Therapy Of HIV Infection During Pregnancy.](#)

This study will enroll HIV infected women who choose to initiate therapy during pregnancy. HIV-1 infected pregnant women at 10-30 weeks gestation are eligible if they are naïve to antiretroviral therapy (other than ≤ 8 weeks of zidovudine), and have an HIV RNA PCR $> 1,000$ copies/ml. They will be randomized to Zidovudine, Lamivudine and Nelfinavir or Zidovudine, Lamivudine and Nevirapine. They will be followed for two years post delivery and their infants will be followed through six months of age.

PACTG 1022 will examine the efficacy of each regimen for virologic suppression in pregnancy and the durability of each regimen for women who initiate antiretroviral therapy in pregnancy. In addition, the study will evaluate adherence and overall health status (as measured by self-report), correlate pre-dose drug levels with adherence, and assess the effect of adherence on viral load and CD4 counts. It will also compare the incidence of abnormal glucose tolerance, gestational diabetes, abnormal lactate levels, abnormal liver function, clinical hepatitis, hypersensitivity reactions and other adverse events during pregnancy between treatment groups, impaired glucose tolerance, diabetes, hyperinsulinemia, and elevated cholesterol and triglycerides postpartum between treatment groups.

[A5084: Evaluation of the Complications Associated with Antiretroviral Medications on HIV Infected Pregnant Women.](#)

This prospective, multi-center, observational study is designed to evaluate the safety and tolerance of antiretroviral

medications in HIV-1 infected pregnant women as measured by metabolic parameters. The study compares 80 pregnant women on protease inhibitor (PI)-containing antiretroviral regimens with 80 on non-PI-containing antiretroviral regimens. No drugs will be dispensed during this study. Candidates are eligible if they are ≥ 13 years of age, between 20 and 34 weeks gestation and have been either on a continuous, stable PI-containing antiretroviral regimen for 8 weeks immediately prior to entry OR not on PI's for 8 weeks immediately prior to entry. They also must anticipate continuing either course for the duration of the study. Subjects will be followed at 8-week intervals from the time of entry until delivery or pregnancy termination, with an additional visit at 12 weeks post-delivery. All infants born to study participants will be evaluated at the time of delivery and at the mothers' 12 weeks post-delivery visit.

A primary goal of the study is to determine whether the relative risk for impaired glucose tolerance (IGT) is increased among HIV-1 infected pregnant women on PI-containing antiretroviral regimens as compared with those on non-PI containing antiretroviral regimens or on no antiretroviral therapy. In addition, the study will examine the effect of antiretroviral regimens on: fasting glucose, insulin, and C-peptide levels; ratio of change in insulin to change in glucose after glucose load; triglycerides and cholesterol; and hemoglobin A1c (HgbA1c). The study will also monitor the influence of the antiretroviral regimens on the incidence of gestational diabetes, postpartum IGT, and postpartum diabetes mellitus. In addition, the study will evaluate whether the frequency of gastrointestinal (GI) symptoms (nausea, vomiting, and diarrhea) is increased among HIV-1 infected pregnant women on PI-containing antiretroviral regimens compared with HIV-1 infected non-pregnant women on PI-containing antiretroviral regimens.

PACTG 1025: The Perinatal Core
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AVRC Updates

Leukoencephalopathy in AIDS Patients: An Emerging Disorder?

By Scott Letendre, MD and Dianne Langford, PhD

HIV can replicate in protected tissue compartments during otherwise successful antiretroviral therapy (ART). This is particularly true in the central nervous system, where penetration of most antiretroviral drugs is limited. Because of this, investigators have remained vigilant for progressive HIV disease of the brain since the introduction of poorly penetrating protease inhibitors.

Recent studies support that brain complications continue to develop in HIV-infected patients taking ART. For example, neuro-imaging studies have found that patients who are treated with potent ARV therapy frequently have focal white matter lesions. In a prevalence study of HIV-associated brain disorders, Antinori found that 8% of ARV-experienced patients had white matter disease (leukoencephalopathy), which was not attributable to other infections.

Now, UCSD neuropathologist Eliezer Masliah has identified a severe form of leukoencephalopathy in participants of the California NeuroAIDS Tissue Network. Working with other UCSD investigators, Dr. Masliah found 7 patients who died of AIDS, had been evaluated during life, and had severe leukoencephalopathy at autopsy. Six of the 7 had failed multiple antiretrovirals (median number 10). At their last ante-mortem evaluation, all were severely immunosuppressed and HIV replication was poorly controlled in 6. Most had been diagnosed with multiple opportunistic conditions but no single infection was shared among all 7. The 5 with the most severe white matter injury met criteria for HIV-associated dementia. T2-weighted MRI revealed multi-focal white matter hyperintensities in 3 and extensive, diffuse, and more confluent white matter hyperintensity in the other 4.

The white matter destruction found at autopsy was dramatic. Gross examination demonstrated moderate to

severe white matter atrophy. Microscopic examination revealed intense perivascular macrophage infiltration, extensive demyelination, and evidence of very high levels of HIV replication. White matter destruction was so extreme in some cases that myelin was completely absent and axons were severely damaged. Prior to the widespread use of HAART, cases of white matter injury were characterized by less extensive perivascular infiltration and myelin loss, milder white matter atrophy, and lower brain concentrations of HIV. While some opportunistic pathogens, such as JC virus, are known to cause severe white matter injury, no evidence was present of this pathogen or others, including CMV, EBV, HHV6 and 8, VZV, and HSV 1 and 2.

For now, the cause of this disorder

remains unknown. Its emergence in the HAART era strongly argues that potent antiretroviral therapy plays a role in pathogenesis. HIV-associated leukoencephalopathy (HAL) may be a severe form of HIV encephalitis that results when ART both extends a patient's life but does not suppress HIV replication in the brain. Alternatively, leukoencephalopathy may be a CNS correlate of protease inhibitor-associated lipodystrophy since myelin is composed primarily of fat. Many other explanations are possible. UCSD investigators plan to identify additional cases and conduct studies aimed at identifying the etiology of this condition. For more information or to refer patients for evaluation, please call Scott Letendre at (619) 543-4730.

Progress and New Studies in Primary HIV Infection

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variety of chronic viral infections (i.e. EBV, CMV). While the importance of HIV-specific immune responses in controlling HIV replication remains somewhat limited, the importance of virus-specific cellular immune responses in the SIV-infected macaque model has clearly demonstrated:

1) depletion of CD8+ T cells with monoclonal antibody in SIV infection is associated with enhanced viral replication;

2) CD8+ cytotoxic T lymphocyte (CTL) responses exert selective pressure sufficient to generate viral CTL-escape mutants; and

3) SIV vaccine strategies that elicit SIV-specific CTL responses can control viral replication and prevent disease progression. Although HIV-specific immune responses generally diminish in patients with established HIV infection treated with potent ARV therapy, preservation of vigorous HIV-specific immune responses have been observed in acutely treated subjects. The functional role of

these immune responses was suggested following a treatment interruption in these subjects after a period of treatment-associated virologic suppression. Treatment interruption was associated with a significant increase in the magnitude and breadth of HIV-specific CTL responses associated with "control" of viremia (often with plasma RNA levels <500 copies/ml) for greater than 5 months in a subset of these subjects. These data support the evaluation of therapeutic immunization interventions as a strategy to enhance and broaden the immune response in subjects who start therapy during acute HIV infection. Therapeutic immunization may also be associated with fewer potential risks than treatment interruption strategies, such as CD4 depletion and the selection for drug resistant variants.

The UCSD Antiviral Research Center is participating in a Merck-sponsored study to identify and characterize HIV-specific T lymphocyte responses (CD4

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Therapeutic Drug Monitoring

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below or above the optimum level?

E. Once the level is considered inadequate, what intervention should be done to maximize the concentration-dose escalation, PK boosting with ritonavir, change to an alternative agent?

F. How should the levels be interpreted in the face of reduced drug susceptibility? Should the C_{min}/IC_{50} for each agent be the appropriate metric?

G. Do NRTI levels correlate with toxicity?

With these questions in mind, the investigators of the CCTG have initiated a trial of therapeutic drug monitoring, CCTG 578. This trial will attempt to define the populations which might benefit most from monitoring and define the algorithms to interpret drug levels. This study will also look at ways to improve adherence and treatment. Patients, either naïve or experienced to antiretroviral agents, will be randomized to receive a new treatment regimen with

the assistance of TDM or without TDM. Currently, this study is recruiting only patients of the Owen Clinic. The primary goal of the study is to help define who might benefit from TDM, how we can predict who will need TDM and how effective TDM is at achieving the "optimal" drug levels in the blood.

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Progress and New Studies in Primary HIV Infection

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and CD8) among patients who start potent ARV therapy within 14 days of recent HIV infection. The purpose of this project is to identify and characterize a group of patients who will ultimately be enrolled into future protocols designed to test the immunogenicity, safety and efficacy of the therapeutic HIV-1 vaccines that Merck Research Laboratories are currently evaluating in Phase I clinical trials. Subjects who present with possible primary HIV infection will have screening tests done to confirm recent HIV infection status and must be willing to start potent ARV therapy within 14 days of documented acute or recent HIV infection. Patients already established on antiretroviral therapy who have started potent ARV therapy within 14 days of documented acute or recent HIV infection will also be eligible if they have been maintained on continuous suppressive therapy since that time. This observational cohort study to character-

ize HIV-specific immune responses will not involve any interruption of therapy or vaccination of study participants. Study volunteers will be reimbursed for their travel time and possible inconvenience of study participation. It is anticipated that Merck preclinical and Phase I studies of HIV-1 therapeutic vaccine constructs will be completed in mid 2002, and that eligible subjects from this observational cohort study (i.e. those with sustained virologic suppression) will be offered the opportunity to participate the planned therapeutic immunization trial which may include a closely supervised treatment interruption.

Patient Volunteers

In collaboration with our colleagues across the country, we hope to recruit sufficient numbers of patients at the very earliest periods following HIV infection to characterize the role of HIV-specific immune responses and subsequently test the strategy of therapeutic vaccination as

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.

a strategy to augment these potentially protective responses. If you are interested in participating in this study or would like to refer a patient, please call the UCSD Antiviral Research Center at 543-8080 to speak with the screening coordinator for further information. The AVRC website (<http://www.avrc.trials.org>) provides a review of primary HIV infection and frequently asked questions by providers and patients under the tab, "Risky Exposure?" Providers wishing to refer symptomatic high-risk individuals for Acute HIV screening are encouraged to call Dr. Little at 543-8080 (business hours) or 543-6737 (study doctor on call after hours) for further information.

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. (ACTG 5086)

2. **Treatment Intensification** — Add either abacavir or amprenavir + ritonavir to current regimen for patients with low level viral rebound. Previously must have had viral suppression while on current ARV regimen. Now must have an HIV RNA between 500 and 10,000 on the same regimen. No previous use of abacavir or amprenavir for more than 4 weeks. (ACTG 5061)

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.



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Optimal Therapy during Pregnancy

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Protocol is a prospective cohort study that provides a framework for collection and evaluation of data and collection of repository specimens from HIV-infected pregnant and post-partum women and their infants. All HIV-infected women \geq 14 weeks gestation with a viable intrauterine pregnancy who intend to continue the pregnancy, or who have recently delivered a live-born or stillborn infant and are within 7 days after delivery, and who receive care at PACTG or collaborative sites will be eligible for enrollment. Women will be followed until 24 months post-partum and their infants will be followed for 6-12 months.

The primary goal of PACTG 1025 is to enroll pregnant, HIV infected women receiving prenatal care or who deliver at PACTG sites and their children into a study in which clinical and laboratory (virologic, immunologic, and biochemical) data and specimens for repository storage are obtained according to a standardized protocol. This study will not provide medication. It will utilize clinical information and collect specimens to assess the effectiveness and safety of interventions (e.g., antiretroviral therapy and mode of delivery) prescribed for preven-

tion of vertical transmission of HIV and/or for women's health. The study will also assess adherence to antiretroviral therapy among HIV-infected pregnant women during pregnancy and postpartum and its' impact on women's health and vertical transmission, and adherence to chemoprophylaxis in infants. PACTG 1025 will also provide a framework and specimen repository for sub studies that aim to further elucidate risk factors for and mechanisms of vertical transmission of HIV and factors that affect maternal and infant outcomes.

Other perinatal HIV trials available at UCSD include:

PACTG 358 A Phase I Trial of the Safety, Tolerance and Pharmacokinetics of Oral Indinavir Co-administered with Lamivudine and Zidovudine in HIV Infected Pregnant Women During Gestation and Post-partum, and to their Infants Post Maternal Dosing.

PACTG 367 Prospective chart review to define current usage patterns of antiretroviral agents among HIV positive women during the immediate pre-pregnancy period and during the pregnancy. Study will abstract charts and de-

livery records for patients who have delivered since January 1, 1998.

The use of antiretroviral therapy in pregnant women presents a challenge as clinicians and women evaluate the risks and benefits of treatments, timing and choice of therapy. The Public Health Service Guidelines acknowledge the limited availability of safety data and recommend that women should be offered HIV therapy to protect their own health and to prevent vertical transmission. These Guidelines offer summary tables of pre-clinical and clinical data on antiretrovirals, and a range of clinical scenarios with specific treatment and delivery recommendations. To obtain copies of these recommendations contact the HIV/AIDS Treatment Information Service (ATIS), <http://www.hivatis.org> or by phone, 800-448-0440.

For information on UCSD perinatal studies, perinatal HIV consultations or prenatal HIV services, please contact Patricia Franklin, CFNP at 619-543-8080.

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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Two Research Studies of Abdominal Fat Treatment

1. Metformin vs. Rosiglitazone vs. combination (A5082)
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Both studies require HIV RNA less than 10,000.

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