

## **Structured Treatment Interruptions: Why or Why Not?**

by Diane Havlir, MD

*“Make sure that you take every dose of your medication. Do not miss doses of your regimen. Do not take days off from your therapy. If you do, chances that HIV will become resistant to your drugs will greatly increase.”*

Does this sound familiar? If you are a patient, your provider has probably wisely told you this many times. If you are a provider, you have probably reiterated this advice many times. We know only too well that adherence to medication is essential to successfully suppressing HIV replication and achieving immunologic benefits.

So why are people now talking about “drug holidays” or “structured treatment interruptions or STIs?” There are actually several situations where this approach is being tested in the research arena. It is important to emphasize that these approaches are experimental, and that the consequences of stopping or interrupting therapy can be detrimental or dangerous in many situations. STIs are being evaluated in patients with acute or chronic HIV infection who have achieved viral suppression. The rationale for this approach is that exposure to increased levels of HIV antigen in patients who have already responded to HAART could lead to improved immune responses to HIV which would ultimately lead to control of the virus with fewer medications. In essence, a patient’s own virus would “boost” immune responses to HIV. Thus far, results are mixed and more time is needed to determine the value, if any, of this approach.

STIs are also being evaluated in pa-

tients with chronic infection who have achieved viral suppression to determine if response to therapy and immune responses can be maintained in patients who stop and start therapy while striving to maintain CD4 cell counts above a certain threshold. The goal here is to preserve immune function but reduce drug toxicity. While there are solid data to support that interrupting and reintroducing therapy of some regimens does not lead to selection of drug resistant virus in the majority of patients over the short-term, this possibility still remains a concern. Studies are in development to test this strategy which carries many inherent risks, but also could prove to be useful.

Finally, STIs are being tested in the setting of patients with uncontrolled viral replication. The rationale here is entirely different. In patients who have been treated with many different drugs, and who have very highly drug resistant HIV, interruption of therapy will allow repopulation with a predominantly drug sensitive population in approximately two thirds of patients. The wild type virus outgrows the drug resistant virus because it has a slight replication advantage. The drug resistant population is still present, but at lower levels. The theoretical advantage of a STI in this setting is that the response to a new regimen will be enhanced. The risks of STI in this setting are two-fold. First, CD4 cells decline when therapy is interrupted, and second, HIV related complications can occur when therapy is interrupted.

The Treatment Center will be starting a trial soon to evaluate the safety and

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### **Mission Statement**

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

# Lipodystrophy and Mitochondrial Toxicity Update

by Tari Gilbert, MSN C-FNP

HAART, though often effective in treatment of HIV infection, is associated with numerous metabolic toxicities. Although lipodystrophy lacks a formal definition, it is a term commonly applied to a constellation of symptoms that include metabolic changes, morphologic changes and associated conditions. The body changes associated with lipodystrophy involve fat redistribution, primarily peripheral lipoatrophy and/or central fat accumulation. Both PIs and NRTIs are implicated as possible causes of lipodystrophy, but NRTI-containing regimens are more frequently associated with fat wasting vs. fat accumulation.

Also associated with lipodystrophy, especially NRTI-associated lipodystrophy, are metabolic changes such as elevated lactate, anion gap and C-peptide levels. Metabolic abnormalities of elevated cholesterol and triglyceride levels are more often seen with PI-containing regimens. Several other

conditions are also hypothesized to be related to lipodystrophy syndrome. These include atherosclerotic cardiac disease, hypertension, osteopenia, and glucose intolerance.

NRTI-associated lipodystrophy can include liver dysfunction, hyperlactatemia, and associated clinical symptoms, such as abdominal pain and bloating, tachycardia, dyspnea, nausea & vomiting, and altered mental status. These are indicative of mitochondrial toxicity, a potentially fatal condition.

A rare disorder, mitochondrial toxicity occurs in the presence of NRTIs, which inhibit an enzyme responsible for replication of the HIV-1 virus. This inhibition does not affect human enzymes, except for the enzyme responsible for mitochondrial DNA replication. When normal mitochondrial functions are disrupted and ATP synthesis becomes less

see *Lipodystrophy* on page 5

## UCSD HIV Research Centers Open House

Celebrating the new location of  
The UCSD Treatment Center, HNRC,  
The Mother & Child Adolescent Program and the Eye Clinic

Please join us;  
Friday October 13, 2000  
150 West Washington  
(NE corner of Washington & Front St.)  
(Parking behind the building)

We gratefully acknowledge the contributions of the following supporters to make this event possible:  
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# Tenofovir, a Novel Nucleotide Reverse Transcriptase Inhibitor

by Scott Letendre, M.D.

The ability of HIV to develop resistance to antiretrovirals (ARVs) has limited the gains achieved by combination therapy. Cross-resistance within classes of agents functionally reduces the number of drugs available for inclusion in new regimens. While second-generation protease inhibitors (PIs), such as lopinavir, have activity against some strains that are resistant to the currently licensed PIs, there are few options for the treatment of HIV strains resistant to multiple nucleoside analogue reverse transcriptase inhibitors (NRTIs). One investigational drug, tenofovir, has activity against many NRTI-resistant strains and, therefore, may be an important new weapon in the armamentarium of the HIV-treating physician.

Tenofovir (TFV), also known as PMPA, is a nucleotide, rather than nucleoside, analogue RTI. Due to limited bioavailability when taken orally, it is administered as a pro-drug, tenofovir disoproxil fumarate (TDF). TFV is eliminated by the kidney, is not metabolized by the liver, and has no cytochrome P450 interactions which complicate the metabolism of PIs. Intracellularly, TFV needs phosphorylation only twice to be active, rather than thrice as with NRTIs. This intracellular product, PMPApp, has a long intracellular half-life (allowing once-daily dosing) and inhibits HIV-1 at much lower concentrations (200 to 3,000-fold) than needed to inhibit human DNA polymerases. TFV also has activity against HIV-2 and hepatitis B virus.

One of the striking characteristics of TFV is its activity against HIV strains that are resistant to NRTIs. For example, HIV strains that are resistant to zidovudine, didanosine (ddI), and dideoxycytidine (ddC) remain susceptible to TFV. TFV even retains activity against strains with the multi-NRTI resistance mutation (Q151M). Lamivudine-resistant strains (M184V) actually exhibit increased susceptibility to TFV.

Conversely, TFV seems to induce little resistance. Scientists were able to derive a strain with decreased susceptibility to TFV in vitro but this required serial passage in MT-2 cells in the presence of increasing drug concentrations. This

mutant exhibited the K65R genotype, which is also associated with the use of ddI, ddC, and abacavir, but only resulted in a 3-fold reduced susceptibility to TFV. K65R has been found in less than 2% of ARV-experienced patients but has been isolated from SIV-infected animals treated with TFV. Thus, the only known TFV resistant mutant form is both uncommon and not very resistant.

In pre-clinical studies, monotherapy with 300 mg TDF once daily reduced HIV RNA levels more than 1 log<sub>10</sub> copies/ml in ARV-experienced and 1.5 log<sub>10</sub> in ARV-naive patients. The efficacy and safety of TDF in combination with other ARVs were examined in a phase 2, dose-ranging study of 189 ARV-experienced patients. In this study, TDF was added to the regimens of patients on stable, but incompletely effective, ARV therapy. Subjects had extensive ARV experience (mean, 4.6 years of therapy) and baseline genotype analyses demonstrated NRTI-associated resistance mutations in 97% of subjects. Despite this, the addition of 300

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# STI

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effectiveness of STI for patients with multi-drug resistant virus. Patients with extensive prior antiretroviral experience, CD4 cell counts greater than 150 cells/mm<sup>3</sup> and HIV RNA greater than 10,000 copies/ml will be eligible. Subjects will have genotypic and phenotypic resistance testing and the “best available” regimen will be selected by their provider based on these results. Then patients will be randomized to either start the new regimen immediately or to take a STI for 16 weeks. During the 16 weeks of therapy interruption, patients will be monitored closely and will start therapy before 16 weeks if the CD4 cell count drops significantly. Patients will be followed for at least a year.

STIs represent a novel approach to treating HIV disease in a variety of clinical settings. Because of the inherent risks, STI strategies merit rigorous evaluation in clinical trials before widespread application in the clinic. If you would like to refer a patient to the study described above or are interested in more information on this topic, please contact the Screening Coordinator at 619-543-8080.

**A special  
“Thank you”  
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UCSD HIV  
Research Centers**

## 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.

**Call Scott Holder to find out more: (619) 543-5020**

**HIV Neurobehavioral Research Center  
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## Tenofovir

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mg TDF daily resulted in a mean HIV RNA reduction of approximately 0.7 log<sub>10</sub> copies/ml at 48 weeks. At the end of the placebo phase (24 weeks), the adverse events in the TDF arm did not differ significantly from placebo and the rates of discontinuation were similar in all arms. After 48 weeks, no patients had confirmed elevations (increase of 0.5 mg/dl over baseline) of serum creatinine.

The UCSD Treatment Center is currently recruiting ARV-naive patients for a phase 3, multicenter, clinical trial of TDF (GS-903). Eligible subjects will receive combination therapy with efavirenz, lamivudine, and either stavudine or TDF. This 48-week study will be actively controlled so that subjects will receive either TDF or stavudine placebo along with the active study drugs. Although subjects must have more than 5,000 HIV RNA copies/ml at entry, there is no CD4 count limitation. Enrolled subjects will be followed at least every 4 weeks throughout the course of the study. As an additional benefit of participation, enrolled subjects will receive studies of bone integrity, such as bone-related biomarkers and regularly scheduled DXA scans.

In summary, TDF is a once-daily nucleotide RTI with excellent activity against multi-NRTI resistant HIV strains and excellent tolerability. It is now available at UCSD in combination with 2 licensed ARVs in a new protocol for ARV-naive patients. Questions about the protocol or referrals may be directed to the screening coordinator at (619) 543-

efficient, lactate and fatty acid can accumulate. Hyperlactatemia, or lactic acidosis, causes the symptoms described above and can lead to liver failure and death. Treatment includes reduction or discontinuation of HAART, and supportive measures.

TARHEEL (Trial to Access the Regression of Hyperlactatemia and to Evaluate the regression of Established Lipodystrophy) is a phase IV, open label, switch design study developed to assess regression of lipodystrophy and/or mitochondrial toxicity, specifically hyperlactatemia. The study will evaluate and manage HIV-1-positive subjects whose viral loads are undetectable (<400 copies/mL) and who have either lipodystrophy symptoms and/or hyperlactatemia. Subjects must have been on a d4T-containing regimen for at least 6 months prior to study onset; d4T will be replaced by a new NRTI (Abacavir, Combivir, Zidovudine, Efavirenz) which will be supplied by the study.

Participants will be followed for 48 weeks with regular examinations, lab work including HIV-1 RNA testing and CD4 counts, periodic DEXA scans, and other measurements. CT scans to assess abdominal adipose tissue will be obtained at baseline and week 48. A small substudy will evaluate mitochondrial function through muscle, fat and liver biopsies. If you are interested in participating in or referring a patient to TARHEEL, please call UCSD Treatment Center at 619-543-8080 and ask for the screening coordinator.

**Research Study:  
Switch Regimens  
in individuals 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**

**Clinical  
Trials  
101**

by

**Susan Little, MD**

**Learn the nuts and bolts of  
HIV Treatment Research  
Sponsored by the  
UCSD Treatment Center  
Community Advisory Board  
November 6th at 5:30 PM**

**150 West Washington Street, Suite 100  
(NE corner of Washington & Front St.)  
(Parking behind the building)**

**Call Jack or Gerry at  
619-543-8080**

**For more information**

**Merck Therapeutic Vaccine Study  
HIV-1 gag DNA vaccine**

**Purpose:**

To establish the safety and tolerability of a HIV vaccine in individuals who have achieved viral suppression on HAART

**Inclusion criteria:**

- 2 years undetectable and on antiretroviral treatment (RNA < 400)
- CD4 cells greater than 500 and never less than 200

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

**TENOFOVIR RESEARCH STUDY  
FOR TREATMENT NAÏVE INDIVIDUALS**

**Tenofovir + 3TC + efavirenz  
vs.  
d4T + 3TC + efavirenz**

**Inclusion criteria:**

- Treatment Naive
- HIV RNA > 5000

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

The UCSD Treatment Center is seeking individuals who are at risk for CMV for a research study (ACTG 5030)

**Inclusion Criteria:**

- ◇ CMV antibody positive
- ◇ CD4 <100
- ◇ HIV RNA >400
- ◇ Receiving HAART or not planning to start HAART for at least 3 months

**Patients receive:**

- ◇ CMV viremia screening every 8 weeks
- ◇ Eye exams every 6 months (every 8 weeks if CMV viremic)
- ◇ Valganciclovir vs. placebo when CMV viremia is detected

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

We would like to thank the following:

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Roche Laboratories**

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**ADHERENCE RESEARCH  
STUDY (AEH 003)**

**MAXIMALLY ASSISTED THERAPY (direct observation) vs. SELF-ADMINISTERED THERAPY**

**Inclusion criteria:**

- Treatment Naive
- CD4 >100

All patients receive ddI, d4T, efavirenz, and nelfinavir

*For more information call (619) 543-8080 and ask for the Screening Coordinator*

**RESEARCH STUDIES AVAILABLE FOR  
ANTIRETROVIRAL-EXPERIENCED INDIVIDUALS**

1. **High Dose ABT 378 (lopinavir) Study** — Evaluate escalating dosing of lopinavir/ritonavir in patients to see if PI resistance can be overcome. Regimen includes lopinavir, ritonavir and up to three NRTIs. Must have experience with at least two protease inhibitors and one NRTI. CD4 count must be less than 200 and viral load more than 1000 copies/mL.
2. **Salvage Study for PI, NNRTI experienced patients with treatment to include tenofovir** — uses amprenavir + ritonavir + abacavir + another NRTI (based on phenotype results) + either tenofovir or efavirenz. CD4 count must be more than 50 and viral load >1000 copies/mL. (*PEARL*)
3. **Salvage Study for PI experienced patients** — compares two dosages of indinavir + ritonavir + 2 NRTIs. Must be naïve to indinavir and ritonavir. Viral load must be between 1000 and 50,000 copies/mL (*ACTG 5055*).
4. **DAPD Study** — adds DAPD (an experimental NRTI) to current regimen. Must currently be on antiretroviral therapy and have past experience with AZT/3TC or d4T/3TC. This is a phase 1, 15-day study. Viral load between 5000 and 250,000. CD4 count must be more than 50 copies/mL.

**For information on any of the above studies,  
call the screening coordinator at (619) 543-8080**



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