

# WOMEN'S INTERAGENCY HIV STUDY

## SECTION 23: METABOLIC TOXICITY SUBSTUDY PROTOCOL (CROSS-SECTIONAL)

### A. HYPOTHESES

**Hypothesis 1:** The point prevalence of osteoporosis will be three- to four-fold higher in HIV-infected women compared to HIV-uninfected women, or HIV-infected women not receiving protease inhibitors.

**Hypothesis 2:** The prevalence of a fasting blood glucose >126 mg/dl, or an elevated fasting serum insulin determination, will be three-fold higher in women receiving protease inhibitor therapy, compared to women (with or without HIV infection) not receiving such therapy, independent of BMI, but not independent of body fat distribution, as determined by DXA scanning.

**Hypothesis 3:** There will not be an increased prevalence of abnormal (>130 mg/dl) low-density lipoprotein (LDL) cholesterol or total cholesterol in women receiving protease inhibitors.

### B. SCIENTIFIC AIMS

**Aim 1:** Determine the bone density and fat distribution by whole body dual x-ray absorptiometry (DXA) scanning of up to 300 women enrolled in the Bronx/NYC and San Francisco consortia.

**Aim 2:** Determine menopausal status of enrolled women through measurement of follicle stimulating hormone (FSH) and estradiol within two days of initiation of menses.

**Aim 3:** Measure fasting insulin, blood glucose and lipid profiles in participating women.

### C. BACKGROUND

The introduction of HIV protease inhibitors and highly active antiretroviral therapy (HAART) has resulted in dramatic improvements in HIV-related morbidity and mortality. However, unforeseen complications have developed in individuals utilizing these highly effective pharmacologic agents, including fat redistribution syndromes, development of insulin resistance (IR) or frank diabetes mellitus (DM) and abnormal serum lipid profiles. Very recently, a newly described complication has been reported in HIV-infected men receiving these agents. Two groups reported at the 7<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (February 2000, San Francisco) findings of an increased prevalence of osteoporosis and osteopenia in cross-sectional investigations of HIV-infected men receiving protease inhibitors (1,2).

In the general population, osteoporosis is a condition common in postmenopausal women, and is associated with significant morbidity and mortality. It is thus important to determine if the findings of an association of osteoporosis with protease inhibitor use in HIV-infected men manifests as the "premature" development of osteoporosis in HIV-infected women, who by virtue of their gender are already at risk for the development of osteoporosis and its complications.

The fat redistribution syndromes and metabolic abnormalities associated with HAART, with or without a PI, have not been well described in women. There is a higher prevalence of IR and DM in women, and particularly women of color, who are disproportionately represented among HIV-infected women in the United States. Preliminary WIHS data has demonstrated a relative risk of three for the development of self-reported incident DM in women receiving protease inhibitor therapy. The expected increase in cardiovascular morbidity and mortality from a three-fold increase in the incidence of DM is substantial. In addition, the lipid profiles of premenopausal women differ from those in men, and changes in fat redistribution and lipid profiles are associated with HIV infection and its treatment in women. Because of the potential implications for the development of

cardiovascular and other complications, it is critical to define further the prevalence of these adverse effects of treatment in women.

#### **D. METHODS**

For the groups of women defined above, bone mineral densities (BMD) and T- and Z- scores by DXA scans (lumbar spine and hip) will be performed at the Albert Einstein College of Medicine Osteoporosis Research Unit in the Bronx, NY, or at The University of California San Francisco. Osteopenia is defined as a T-score between -1 and -2.5, and osteoporosis as a T-score less than -2.5. Fasting blood samples will be taken for insulin, glucose, lipid profile, FSH and estradiol. A two-hour glucose tolerance test will be administered in addition to fasting bloods. A single random specimen of urine, and one additional 8 cc tube of whole blood will be collected and frozen (after separation of the blood for serum) for possible future use for determination of markers of bone turnover or other studies. Historical information will be collected, including clinical factors that are associated with osteoporosis, such as smoking tobacco, alcohol and caffeine intake, activity level, age of menarche, family history of osteoporosis.

#### **E. STUDY PROCEDURES**

##### **BRONX**

##### **1. PRIOR TO CORE VISIT**

The study coordinator must check the eligibility list against v13 data to confirm:

- If participant weight is over 264 pounds, she should be excluded.
- HAART category
- If participant has type I diabetes (F22, C31, d1), she should be excluded
- If participant is eligible she can be informed about the study when confirming her core visit and asked to bring her HAART and HRT medications to verify usage.

##### **2. AT CORE VISIT PRIOR TO SCREENING**

The study coordinator must check with clinician (or Form L12) to see if the participant is pregnant. If yes, do not proceed with screening. If no, proceed with screening.

##### **3. SCREENING**

The study coordinator administers the Screening Form. After the participant's eligibility is confirmed, the participant is given a consent form to sign and given a copy of the consent. Brooklyn participants will be consented at DXA/GTT visit.

##### **4. AFTER SCREENING**

If the participant is eligible, the study coordinator will give her a letter with instructions, a menstrual calendar and an appointment for DXA scan and GTT. In the Bronx, appointments can only be scheduled for Fridays during Visit 14. The study coordinator will schedule the participant for the first Friday available.

On odd visits, the study coordinator will copy Form 31 from the core visit prior to screening and put it in file to have a record of urine collection for possible later TNx assay, if needed. On even visits, aliquot 5 ml of urine from the pregnancy test, freeze and store in Bronx repository.

##### **5. DAY BEFORE DXA/GTT VISIT**

The study coordinator must call the participant to remind her to fast, and to bring her menstrual calendar. If the participant has started HRT, she is to be excluded. If there is a lapse of more than three weeks since the participant was consented then she can be screened for steroids on the

phone. If she has been on oral steroids at the exclusionary dosage, then the participant will not be eligible to be in the study. If the participant is still eligible and if she is menstruating and between days two and six of menses, she can have blood drawn for FSH/Estradiol during the DXA/GTT visit. The study coordinator will indicate that on MTSVCS form. The participant will be asked to bring her HAART medication to the visit so that any changes since her core last core can be verified.

#### 6. AT DXA/GTT VISIT

If the participant is not menstruating and is not within the first two weeks post menses she must be screened for pregnancy prior to administration of the Confirmation Form. If pregnant, she is no longer eligible.

##### a. Confirmation Form

If the participant has eaten within the last eight hours, the phlebotomist must be informed. The participant cannot have GTT test or DXA.

- Since there will be a gap in time (even a few day) between initial screening and the DXA visit it is important to administer the Confirmation Form to document any changes in PI/HAART regimen. If the participant is not eligible for the hormone blood draw, the study coordinator will look at the participant's menstrual calendar and project the time she may be eligible to come in for her hormone blood draw (one tube for FSH/estradiol).

##### b. Medical History Form

This form may be administered after the Confirmation Form.

#### 7. DXA SCAN

The DXA technician is given Form MTS 004 with participant ID, DOB and ethnicity filled out. The participant is weighed and measured. The participant receives regional (hip and lumbar spine) and whole body DXA. The entire procedure should take between 20 and 40 minutes. An electronic copy of the data file generated from the whole body scan will be transmitted to UCSF. Regional scan results from UCSF will be transmitted to the Bronx.

#### 8. SPECIMEN COLLECTION AND GTT

**Note:** For Bronx all red top tubes must be 10ml size.

The phlebotomist does the first blood draw and fills out the Specimen Collection Form. If the participant is menstruating, the phlebotomist will draw a tube for FSH/estradiol testing. If not, the phlebotomist does not draw that tube of blood. If the participant is not diabetic, the phlebotomist will proceed with administration of the 75g glucose load.

- The participant must drink the entire contents of the bottle within about five minutes. The timer is set. At 30 minutes, 60 minutes, 90 minutes and at two hours, the phlebotomist proceeds with the blood draw according to protocol.
- Three extra tubes are to be collected for possible future use for determination of C-peptide and pro-insulin markers of bone turnover. They are to be collected as follows: first one at fasting, second one at 30 minutes, the last one at 120 minutes.
- When the last blood draw is completed, the participant is given a snack (or money for a snack) and can go home.

## **SAN FRANCISCO**

**Note:** Study procedures for San Francisco have been developed locally.

### **1. PROCESSING AND LABELING PROCEDURES**

Specimens from San Francisco are to be processed according to protocol and labeled with the following information: Pt. ID, visit date, visit #, specimen and time of draw. These are still in the process of being developed with the Montefiore lab.

### **2. SHIPPING MANIFESTS**

Only those specimens that are to be tested at Montefiore should be shipped from San Francisco to Montefiore and should be accompanied by an invoice indicating contents (specimen list), date of shipment, conditions, and destinations. A Montefiore requisition form should accompany the specimens. The specimen list should be prepared in the grid format (unless otherwise specified by Montefiore). An electronic copy of the specimen list should be emailed to Esther Robison ([erobi220@aol.com](mailto:erobi220@aol.com)) at the time of each shipment. A cover letter should be sent with the specimens stating that these are for the Metabolic Toxicities Study, the total number of specimens, and a contact number with phone and pager numbers.

## **F. DATA ANALYSIS**

Assuming a baseline group prevalence of 10% abnormal bone density in the control group (HIV-uninfected women) and an odds ratio of 3.0, 97 women are needed in each group to detect a difference with power of 0.8.

All new data (DXA results) will be double entered locally. Variables needed from the WDMAC database will include demographic characteristics of the participants, and the type and duration of HAART exposure.

Participants will be provided with an incentive as compensation for their time. Results of DXA scans will be provided to the participants, and abnormal results will be communicated both to the woman and to the clinical provider of her choice, verbally and in written form.

## **G. REFERENCES**

1. P. Tebas\*, W. G. Powderly, S. Claxton, D. Marin, W. Tantisiriwat, S. L. Teitelbaum, And K. E. Yarasheski. Accelerated Bone Mineral Loss In Hiv-Infected Participants Receiving Potent Antiretroviral Therapy. 7<sup>TH</sup> Conference on Retroviruses and Opportunistic Infections, San Francisco, February 2000, Abstract # 207.
2. J. Hoy\*<sup>1</sup>, J. Hudson<sup>2</sup>, M. Law<sup>2</sup>, D. A. Cooper<sup>2</sup>. And For The Piir Investigators. Osteopenia In A Randomized, Multicenter Study Of Protease Inhibitor (Pi) Substitution In Participants With The Lipodystrophy Syndrome And Well-Controlled HIV Viremia. 7<sup>TH</sup> Conference on Retroviruses and Opportunistic Infections, San Francisco, February 2000, Abstract # 208.