

Consortium News	page 2
Report Back from CROI	page 3
2006 Membership Renewal	page 11
Clinical Trials Update	page 11
SMART	page 11
Anal Dysplasia	page 12
Neurology	page 12
Opioids and Cannabinoids	page 12
Genomics	page 12
ESPRIT	page 12
FIRST	page 12
LTM	page 13
Oyster Mushrooms	page 13
Staying Well- MBSR	page 13
Other Studies	page 13
Looking for an IRB?	page 15

upcoming conferences

THE 16TH INTERNATIONAL AIDS CONFERENCE (IAC)
August 13-18, 2006
Toronto, Canada
<http://www.aids2006.org/>

THE 46TH INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY
September 27-30, 2006
San Francisco, California
<http://www.icaac.org/>

educational programs

“COMPLEMENTARY THERAPIES IN THE ART ERA: WHAT’S HOT AND WHAT’S NOT”

Wednesday, June 14, 2006
6:00 p.m. – 8:30 p.m.
Genentech Hall, Mission Bay Campus, UCSF

Speakers:
Rick Hecht, MD
Candy Tsourounis, PharmD
Misha Cohen, OMD, LAc
Donald Abrams, MD

“REPORT BACK FROM IAC”

Wednesday, September 6, 2006
6:00 p.m. – 8:30 p.m.
Genentech Hall, Mission Bay Campus, UCSF

Speakers:
Diane Havlir, MD
Steve O’Brien, MD
William Owen, MD

consortium tidbits

Starley Shade, Senior Statistician, has had her abstract “When is the optimal time to change highly active

antiretroviral therapy (HAART): Effect of viral load at the time of treatment change on subsequent CD4+ T cell count using dynamic treatment regimes” selected for poster exhibition at the XVI International AIDS Conference. Starley is about to complete her PhD. in Epidemiology at the University of California-Berkeley. Congrats Dr. Shade!

Congratulations to Hector Vizoso, RN, who graduates with his MSN in Nursing Administration from Cal State. He has been accepted into the Adult Nursing Practitioner program at UCSF in HIV/AIDS.

Donald Abrams, MD, and Paul Couey will attend the first North American Research Conference on Complementary and Integrative Medicine in Edmonton, Alberta, May 24-27, 2006. Posters from the vaporized marijuana study and the oyster mushroom study will be presented, and Donald will give an oral presentation on the results of the dehydroepiandrosterone (DHEA) study. If you can’t make it to Edmonton, you will be able to get a summary of this information at the upcoming June 14th CME program.

The Consortium welcomes Claire Rappoport. She is working with the newly formed International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) HIV/AIDS clinical trial network as their community liaison. The Community Liaison is responsible for providing administrative and analytical support to the INSIGHT Network by focusing on international community representation and participation. Currently, INSIGHT is active in 34 countries with over 400 sites. Claire, for many years our Community Advisory Board chair and representative to the CPCRA Community Constituency Group, is no stranger to the Consortium

office! She can now be reached at: 476-9554 x319, crappoport@php.ucsf.edu.

community advisory board

The Community Consortium Advisory Board (CAB) is looking for new members to participate in providing community input regarding Community Consortium clinical trials. The Board meets quarterly at the Consortium office. The next meeting is scheduled for Monday, August 21, 2006 at 12 p.m. If you know individuals who might be interested, please have them contact Steve Murray, 415-476-9554 x305 or smurray@php.ucsf.edu

executive advisory board

The next Executive Advisory Board meetings are scheduled for Wednesday, July 19 and October 25, 7:30 a.m.

Happy Spring!



Donald I. Abrams, M.D.,
Editor



Paul Couey
Contributing writer

On February 22, 2006, the Community Consortium presented its annual *Report Back From CROI*, a presentation of highlights from the Conference on Retroviruses and Opportunistic Infections, which took place February 5-8 in Denver, CO. Donald Abrams, MD, Chair of the Consortium, moderated the event. The featured speakers were Steven Deeks, MD, Associate Professor of Medicine at the UCSF Positive Health Program at San Francisco General Hospital, Stephen Follansbee, MD, Director of Kaiser San Francisco HIV Services, and Kathleen Mulligan, PhD, Assistant Adjunct Professor at UCSF.

SMART Summary

Dr. Abrams began the evening with a discussion of the recent closure to enrollment in SMART, an international study comparing two “Strategies for Management of Anti-Retroviral Therapy.” This enormous trial includes 112 patients accrued locally through the Consortium and over 5000 participants worldwide. While meeting in Sydney in January to discuss future science, the protocol team received a faxed message from the NIH regarding a safety concern noted by the study’s Data and Safety Monitoring Board (DSMB). The message directed that enrollment cease immediately, though it suggested that the study itself, once adequately modified, might be allowed to continue.

Some of the data that led to halting enrollment were presented in Denver (El-Sadr et al.). In the trial, patients with CD4+ T cell counts >350 cells/mm³ were randomized to either the drug conservation (DC) arm or the viral suppression (VS) arm. In the DC arm, patients remained off ART until the CD4+ count fell to <250 cells/mm³, at which time they initiated or resumed therapy, and stopped again when the count climbed to >350 cells/mm³. They were thus expected to oscillate between 250 and 350 cells/mm³. In the VS

arm, patients initiated or resumed continuous ART with the aim of achieving maximal viral suppression. The primary endpoint was HIV disease progression or death; other key endpoints were death itself, serious HIV progression events, and severe complications (grouped as cardiovascular, renal, or hepatic). The expected duration of the study was 8 years, allowing for 910 endpoints; however, the DSMB detected a safety concern after the development of only 164 endpoints in a mean 14 months of follow-up. As of January 11 when enrollment stopped, the study had accrued 5472 of a projected 6000 patients, from 318 sites in 33 countries. Dr. Abrams noted that part of SMART’s rationale was that the DC strategy might benefit resource-poor countries by sparing them some of the costs of continuous antiretroviral therapy.

Reviewing baseline characteristics, Dr. Abrams noted that the two arms were well balanced, with CD4+ cell counts close to 600 cells/mm³ and median nadir CD4+ counts of 250/mm³. The majority of patients had viral loads <400 copies/mL. In both arms approximately a quarter of those enrolled had had an AIDS-defining diagnosis. Though antiretroviral-naive patients were eligible for enrollment, less than 5% were naive

at entry; on average patients in both arms had 6 years of prior antiretroviral experience.

In the VS group, in which antiretroviral treatment was supposed to continue without interruption, approximately 90% did in fact maintain therapy past month 36. In the DC arm antiretroviral use steadily increased, such that about 60% of patients at month 36 were on therapy. As expected, the amount of follow-up time in which patients were below the 350 cells/mm³ CD4+ count threshold was far higher in the DC group than in the VS group; it was also significantly higher for both the 250 cells/mm³ and 200 cells/mm³ thresholds. In the DC group, the rate of clinical progression or death (per 100 person-years) was 3.7 (n=117), compared to 1.5 (n=47) in the VS group, and the relative risk was 2.5 (thus, DC patients had a 2.5-fold increased risk of disease progression or death). This result was highly statistically significant. Dr. Abrams recalled ACTG 019, a study of AZT in patients with <500 CD4+ cells/mm³, which showed that 7% of placebo patients experienced disease progression over one year of follow-up compared to 4% of patients on AZT. As he pointed out at the time, this meant that 93% of placebo patients did *not* progress. Similarly, though the DC arm of SMART was stopped because the rate of progression was twice that of the VS arm, it is notable that 96% of DC patients did not progress. Nonetheless, biostatisticians have clearly demonstrated that it would be impossible over time for the DC group ever to catch up to the VS

group and thereby achieve equivalence as a treatment strategy. In fact, relative risk analysis for all endpoints favored the VS strategy. To the surprise of many, the relative risk of serious events that had been considered complications of HIV therapy (cardiac, renal, or liver) was actually greater in the DC arm.

In summary, the DC arm, compared to the VS arm, is associated with increased risk of HIV disease (including death), death, serious HIV disease progression, and severe complications. The risk of disease progression or death in the DC arm vs. the VS arm did not differ by nadir CD4+ cell count, and was three-fold higher among patients on antiretroviral therapy at baseline with viral loads <400 copies/mL compared to patients on antiretroviral therapy at baseline with viral loads >400 copies/mL. For all other subgroups examined, risk was greater for those in the DC arm. The conclusion of the SMART study investigators, then, is that episodic use of antiretroviral therapy based on CD4+ cell count levels *as per the SMART study design* is inferior to continuous therapy for the management of treatment-experienced patients, and it is not a recommended strategy. They advised that it would be prudent for all DC patients to resume antiretroviral therapy if they have not already done so. They hope to determine, in continued follow-up, the length of time needed for DC patients who restart therapy to catch up to those in the VS group.

Dr. Abrams, in yielding the podium to Dr. Deeks, asked for his comments on SMART and on the conference as a whole.

Regarding SMART, Dr. Deeks responded that perhaps the most interesting observation was the increased risk of unexpected non-HIV complications associated with treatment interruption. The

theory during the study design and implementation was that the patients on continuous therapy would be more likely to suffer liver, renal, and cardiovascular disease. That in fact the opposite was found to be true may provide some significant insights into the nature of the HIV disease process. The probable mechanism driving the increase in risk, he feels, is inflammation associated with interrupting therapy. Stopping a treatment regimen, particularly an effective one, has “violent consequences”; there is generally a period of several months in which increasing viral load and T-cell activation cause chaos. Various published reports have suggested that this inflammation is quite dangerous, particularly with regard to cardiovascular processes. He hopes, he said, that the SMART team focuses on this mechanistic question as the study is redesigned.

“Observations of Interest”

To provide his overall impressions of the conference Dr. Deeks referred to his personal list of the “Top 10 or So Observations of Interest to Me” – the ideas he most enjoyed thinking and talking about:

- Massive CD4+ T cell depletion occurs in the gut during primary infection, but this may have no clinical relevance.
- Elite controllers: long-term non-progression may be half due to T cell response, half due to something else, currently unknown.
- Treatment interruptions are associated with short-term risk of non-HIV related complications, including cardiovascular events. Atherosclerosis is predicted by CMV responses.

- Cardiovascular events are higher in PI-treated patients than in those not treated with a PI. This is not fully explained by lipid changes; it may have to do with insulin resistance.
- TMC 114 response is predicted by five discrete mutations, all of which emerge during failure.
- TMC 125 response is greatly diminished with 3 or more NNRTI mutations. NNRTIs should not be continued during virologic failure.
- Unboosted atazanavir is nearly as effective as boosted atazanavir, and may work as monotherapy.
- HLA B57 screening may prevent or greatly reduce abacavir hypersensitivity in clinical situations.
- Tenofovir toxicity is rare in patients with normal renal function at baseline who have early stage disease and who have not taken concomitant nephrotoxic medications; tenofovir causes modest decreases in creatinine clearance in other patient populations.
- Integrase inhibitors are well-tolerated and work over 16 weeks.
- R5 inhibitor failure is not associated with universal shifts in co-receptor tropism. Long-term incomplete viral suppression on HAART is associated with greater prevalence of X4 virus. Presence of X4/dual tropic virus is not predictive of rapid CD4+

declines in the setting of treatment.

Clinical Trials of Atazanavir

There were two studies of existing antiretroviral agents that were of interest to Dr. Deeks, and both concerned the PI atazanavir (ATV). He noted that for many providers ritonavir-boosted atazanavir (ATV/r) has become the first-line PI of choice, despite the lack of data on the activity of ATV/r from treatment-naïve studies. Malan et al. presented results from BMS 089, which randomized antiretroviral-naïve patients to either ATV/r (n=95) or ATV alone (n=105) with a background regimen of extended-release d4T + 3TC, all taken once daily. The study is ongoing, though the presentation was based on 48-week results. The study's primary endpoint was the proportion of subjects with HIV RNA <400 copies/mL through week 48; planned secondary assessments included proportion with HIV RNA <50 copies/mL, CD4+ count change, and safety parameters. The study is underpowered, said Dr. Deeks, and, though it was designed to show "non-inferiority," the results seem inconclusive. Three patients experienced virologic failure in the ATV/r arm, compared to 10 in the ATV arm; none of the ATV/r patients were found to have PI resistance, compared to 3 ATV patients. One ATV/r patient displayed the M184V mutation, the harbinger of limitations in treatment options, compared to 7 ATV patients. None of these differences were statistically significant; however, Dr. Deeks suggested, a better-designed study with several hundred patients on each arm would likely show that the two arms were acting quite differently from a statistical perspective. As expected, there were more adverse events in the ATV/r arm. AE-related discontinuations were brought on primarily by jaundice and scleral icterus (22% and

23% in the ATV/r arm; 7% and 13% in the ATV arm). Part of the analysis for the study was devoted to a comparison of lipid changes between arms over 48 weeks. The study indicates that ritonavir, even at 100 mg once a day, is associated with lipid derangement: changes in both total cholesterol (+15% vs. +6%) and triglycerides (+26% vs. -3%) were greater in the ATV/r arm. But despite the toxicities, said Dr. Deeks, he remains a big fan of boosted atazanavir, and this study more or less confirms its efficacy and safety.

Another study of interest is ACTG 5201 (Swindells et al.), a single-arm pilot study in which aviremic patients (viral loads <50 copies/mL) with CD4+ cell counts ≥ 250 cells/mm³ and no history of virologic failure (n=34) discontinued their nucleoside analogs and started ATV/r monotherapy. Over the subsequent 24 weeks, there were 3 patients with virologic failure, none of whom showed any PI mutations. Two had no measurable ATV at the time of failure, leading investigators to conclude that they had been nonadherent. As with previous, similar pilot studies of lopinavir/r, the investigators feel these results support proceeding with a larger randomized trial that could establish nucleoside-sparing regimens as a reasonable treatment option.

Ritonavir-Fluticasone Interaction

Dr. Follansbee spoke next, opening with the observation that the areas of investigation represented at CROI are becoming more complex, and may be difficult for the average clinician to comprehend. He recommended consulting the CROI website (www.retroconference.org), particularly

the webcasts, for further explication of the more esoteric topics. He had decided, he said, to talk about a few of the presentations that seemed useful to his daily clinical practice.

The first such presentation concerned ritonavir and fluticasone. Abbott added a warning to the ritonavir package insert last year that RTV 100 mg increases the fluticasone C_{max} 26.7 fold and the AUC 368 fold. He had forgotten this warning, Dr. Follansbee said, and a female patient in his practice on the RTV/fluticasone combination developed severe skin friability and bleeding, hyperglycemia, hyperlipidemia, and Cushingoid facial features – all of which resolved within 3 months following discontinuation of fluticasone and adrenal replacement. A Kaiser pharmacologist reminded him of Abbott's warning, and they subsequently reviewed the database of 1800 patients to determine how many were taking both drugs. They identified 29 cases, of which only 3 had shown any clinical manifestations. However, Hull et al. conducted a study in which 50 HIV clinic patients were screened sequentially; 7 had fasting cortisol levels <28nmol/L (cases), and 43 had normal levels (controls). All 7 cases were on the RTV/fluticasone combination; only one control was on the combination. Of the 7 patients with adrenal suppression, 3 were asymptomatic, 2 had Cushingoid features, 1 had easy bruising, and 1 had loss of diabetic control. The high incidence of cortisol suppression and associated symptoms underscores the need for diligent follow-up among patients

taking the two drugs together. The combination should be avoided if possible; if not, routine fasting cortisol screening is in order.

Cardiovascular Disease

Dr. Mulligan's first remarks concerned longitudinal cardiovascular disease (CVD) data from several cohorts (the D:A:D study, the Kaiser Northern California cohort, the Nutrition for Healthy Living cohort, and ACTG 5078), cross-sectional data from the SCOPE study, and results of a study of treatment with fish oil and fenofibrate.

D:A:D is a vast international cohort that started when CVD symptoms in HIV patients were first beginning to be appreciated and has thus compiled data from many years of follow-up. The presentation at CROI focused on relative risk of myocardial infarction associated with PIs and NNRTIs (Friis-Møller et al.) Risk of MI among patients in the cohort has actually decreased over time (1999 through February 2005); however, PI use is related to risk of MI, and incidence of MI increases with each year of PI exposure. Adjustment for hyperlipidemia only partially reduced the effect of PI exposure. The investigators did not find evidence that increased NNRTI exposure is associated with risk of MI.

Klein et al., reporting on data from the Kaiser Northern California cohort, confirmed the increased risk of coronary artery disease and MI associated with HIV disease and particularly with PI use. CVD rates in HIV-infected patients and HIV-negative patients were 6.0 and 2.9 per 1000 person-years, respectively. Age-adjusted relative risk for MI was 1.0 for PI exposure <2 years, 1.5 for PI exposure 2-3.9 years, 1.8 for PI exposure 4-5.9 years, and 1.4 for PI exposure >6 years. The overall relative

risk was 1.16 per year of PI exposure. However, CVD/MI risk has stabilized over 10 years, due to changes in antiretroviral therapy in recent years (e.g., switching to atazanavir, stopping d4T), better management of lipids and blood pressure, and smoking cessation.

Somewhat contrary results from ACTG 5078 were presented (Currier et al.) that cast some doubt on the HIV/PI-CVD relationship. Measuring carotid intima-medial thickness (cIMT), a technique that correlates with coronary artery atherosclerosis and clinical cardiovascular events, the study evaluated 134 patients with a median follow-up of 3 years. Matching for age, sex, race/ethnicity, smoking status, blood pressure status, and menopausal status, patients were enrolled into 3 groups: (1) HIV-infected with >2 years of PI exposure, (2) HIV-infected and PI-naive, and (3) HIV-negative. The PI-experienced group had more metabolic abnormalities at baseline than either of the other groups; however, a comparison of yearly rates of IMT progression showed no statistically significant differences between Groups 1 and 2, between Groups 2 and 3, or between the combined HIV Groups and Group 3. The results did hint that duration of PI use, particularly ritonavir, could accelerate carotid IMT, but the authors suggest that antiretroviral therapy may play a less significant role than other cardiac risk factors in the higher CVD incidence observed in the HIV-infected population.

So are there other risk factors that are disease-specific? Priscilla Hsue et al., making use of the SFGH SCOPE cohort, investigated the possibility that CMV might be associated with increased atherosclerosis in HIV patients. To do this, they performed measurements of

carotid IMT by ultrasound, as well as high sensitivity C-reactive protein (hs-CRP) and T-cell activation assays in 93 HIV-infected patients and in 37 uninfected controls. Both carotid IMT and hs-CRP were higher among the HIV+ patients, and there was a trend toward correlation of the two measurements. CMV-specific T-cell responses were also higher in the HIV+ population, and they correlated significantly with carotid IMT. The authors thus posited that CMV-induced immune responses and/or inflammation may indeed be responsible for accelerating atherosclerosis among HIV+ patients.

Moving on to the topic of hypertriglyceridemia, Dr. Mulligan discussed a presentation from the ACTG 5186 trial, a randomized, open-label study of fish oil 3 mg BID and fenofibrate 160 mg QD for HIV+ patients with triglyceride levels >200 mg/dL (Gerber et al.). Four of 47 patients given fish oil responded (i.e., achieved triglycerides <200 mg/dL) after eight weeks vs. 8 of 48 who were assigned to fenofibrate. However, the baseline triglyceride level in both arms was >650 mg/dL, and there were median reductions of 46% and 58%, respectively. Of 75 “non-responders” given fish oil + fenofibrate for a further 8 weeks, 17 (23%) responded. LDL cholesterol increased with either treatment, but both were generally well tolerated. In substudies the study team found that fish oil had no effect on lymphocyte proliferative response or lopinavir pharmacokinetics. So fish oil, especially combined with

fenofibrate, appears to be an effective treatment for some patients.

Novel Antiretroviral Agents

Dr. Deeks returned to discuss the data presented on agents that have not yet been given FDA approval. One such drug is the 2nd-generation NNRTI etravirine (TMC125), for which the first long-term clinical trial results were presented at ICAAC in December (Grossman et al.). The C223 study enrolled 199 patients with NNRTI resistance and ≥ 3 PI mutations and randomized them 2:2:1 to TMC125 400 mg BID, TMC125 800 mg BID, or active control. The background regimen for the TMC125 arms was Kaletra + T-20 + investigator-selected NRTIs; the active control was the best available regimen from licensed agents. After 24 weeks the two TMC125 arms achieved significantly greater reductions in viral load than the active control arm. At CROI, Vingerhoets et al. presented another analysis from the C223 study, examining the influence of number of baseline NNRTI mutations on virologic response in the TMC125 800 mg BID arm. There was an overall viral load reduction of 1.18 log₁₀ copies/mL in these patients who, at baseline, had a median of 4 primary PI and 2 NNRTI mutations. However, patients with 2 or more mutations fared significantly worse; those with ≥ 3 mutations achieved a mean 0.66 log₁₀ reduction - still substantially higher than in the active control group (-0.19 log₁₀). NNRTI mutations associated with high-level resistance (fold concentration >10) were K101P, V179E, Y181I, Y181I/V, G190S, and M230L.

Tibotec’s protease inhibitor darunavir (TMC114) was also discussed. The drug is expected to receive expedited FDA approval in May or June, based on the POWER 1 and 2 studies. Wilkin et al.

showed results at ICAAC demonstrating its superior potency vs. comparator PIs in PI-resistant patients. At CROI, DeMeyer et al. presented results from a subanalysis of both studies that compared resistance data (genotype and phenotype) at baseline and at 24 weeks to determine the effect of baseline PI susceptibility and on-treatment mutations on TMC114/r or comparator PI efficacy. The study found that the response rate was better in TMC114/r patients than in comparator PI patients, whether the comparator was sensitive or resistant. Baseline mutations that were predictive of decreased TMC114 susceptibility were V32I, L33F, I47V, and I54L alone or with one or two additional mutations; however, it appeared that several mutations were required to alter susceptibility. Interestingly, isolates from patients who rebounded on TMC114 showed no decrease in tipranavir susceptibility.

Dr. Deeks moved on to integrase inhibitors, specifically Gilead’s GS-9137 (DeJesus et al.) and MK-5108, from Merck (Grinsztejn et al.). GS-9137 is in phase 3 of development, MK-5108 in phase 2. They have comparable efficacy, both eliciting an approximate drop in HIV RNA of 2.0 log₁₀ after 10 days of dosing. There is a trade-off, however, in dosing. MK-5108 must be taken twice a day, while GS-9137 can be taken once daily; GS-9137 requires boosting with ritonavir, though, whereas MK-5108 does not. There are as yet no reported drug-related toxicities of significance.

Dr. Deeks next mentioned the three experimental CCR5 inhibitors: aplaviroc (Glaxo SmithKline), maraviroc (Pfizer), and vicriviroc (Schering Plough). Each has experienced delays in the development process. Severe

hepatotoxicity associated with apilaviric resulted in closure of phase 3 studies in both treatment-experienced and treatment-naïve patients. A single case of hepatotoxicity and eventual liver transplant was reported in a patient taking maraviroc, necessitating ad hoc DSMB review and protocol amendment for phase 2 and 3 trials. Vicriviroc (VCV), though, is the only one of the three that raises questions of efficacy. Greaves et al. reported at CROI on protocol P03802, a phase 2 placebo-controlled trial in treatment-naïve subjects with R5-tropic HIV, which demonstrated that VCV is associated with viral breakthrough. Ninety-two patients were randomized to one of 4 arms: VCV at 25 mg QD, 50 mg QD or 75 mg QD, or placebo, each as monotherapy for 2 weeks followed by the addition of Combivir to the VCV arms or Combivir + efavirenz for patients on placebo. The study was designed for a 48-week follow-up period but was prematurely terminated, so that mean follow-up time was 32 weeks. The early closure was based on significantly higher percentages of viral rebound in the VCV arms vs. placebo: 57%, 45%, 22%, and 8%, respectively. The authors noted that pharmacokinetic parameters were as expected, and that tropism shift (R5 to X4) occurred in both treatment and control arms, so neither fully explains the high rate of viral rebound. CCR5 inhibitor failure is not associated with universal shifts in co-receptor tropism, and the presence of X4/dual tropic virus is not predictive of rapid CD4 declines among patients on antiretroviral therapy.

CMV Prevention

Returning to the podium, Dr. Follansbee said that, although the conference now focuses primarily on virology, there were a few presentations on opportunistic infections that were interesting to him. First, ACTG 5030 (Wohl et al.) evaluated the use of valganciclovir for prevention of CMV end-organ disease in patients with CD4+ cell counts <100 cells/mm³ and detectable CMV viremia. In Step 1, the study enrolled 338 patients, 80% of them on HAART, and performed CMV DNA testing by PCR every 8 weeks. Of these patients, 67 were found to be viremic, and 47 were randomized to receive induction and maintenance valganciclovir (n=24) or placebo (n=23) for a median 65 weeks (Step 2). The median CD4+ count among these patients was 12 cells/mm³. Nine patients developed confirmed or probable CMV end-organ disease: 5 receiving valganciclovir, 4 placebo. So although the rate of CMV disease is much lower since the onset of the effective ART era (compared to $>50\%$ before among patients with CD4+ counts <50 cells/mm³), that rate is not nil, and it appears that patients on ART who nonetheless develop CMV viremia derive no benefit from preemptive anti-CMV therapy. Dr. Follansbee observed that these results call into question the clinical utility of CMV PCR screening.

HSV-2 Shedding Rates in HIV Coinfected

Spak et al. presented results of another OI study, an evaluation of HSV-2 reactivation rates in the setting of immune reconstitution following initiation of ART. The study followed rates of HSV shedding in 38 men and 7 women by obtaining daily swabs (penile, vulvar, cervical, and perianal) for three yearly 60-day periods. Viral shedding was quantified by PCR. Of

6412 days of genital swabs, positive HSV-2 rates were 18.5% for men and 22.9% for women; among both men and women with positive samples, 80% were asymptomatic. The highest genital HSV-2 shedding rates occurred within 90 days following ART initiation. For those with CD4+ counts ≤ 200 cells/mm³, the shedding rate within 90 days of starting ART did not differ significantly from those already on ART or those not on ART. Among those with CD4+ counts >200 cells/mm³, the shedding rate within 90 days of ART initiation was significantly higher than for those on established ART or no ART. These results support anecdotal reports of clinical worsening of genital herpes during immune reconstitution inflammatory syndrome. They may also point to a need to reinforce the need for barrier protection among patients, Dr. Follansbee said.

Testosterone gel for visceral adiposity

Dr. Mulligan continued her summary of presentations related to the metabolic syndrome with a discussion of ACTG 5079, a study of testosterone's effect on fat mass and distribution in HIV-infected men with abdominal obesity (Shikuma et al.). The rationale for the study was that (1) HIV-negative men with visceral obesity tend to have low testosterone levels, and (2) replacing testosterone in middle-aged hypogonadal men who are HIV-negative is known to decrease visceral fat while also increasing insulin sensitivity and lowering lipid levels. The study enrolled 88 HIV-positive men with abdominal obesity (waist-to-hip ratio >0.95 or mid-waist circumference >100 cm) and mild to moderate testosterone depletion (serum total testosterone level 125-400 mg/dL or free testosterone level <50 pg/mL) and assigned them to either

testosterone gel 10 g/d or placebo for 24 weeks. Participants underwent single-slice abdominal CT and whole-body DEXA scans at baseline and weeks 12, 24, and 48. In the week 24 results presented, visceral fat change, as measured by CT, did not differ between groups; however, testosterone use was associated with a significant decrease in subcutaneous fat and total abdominal fat compared to placebo. In addition, and also statistically significant, DEXA scanning revealed decreased fat in the trunk and extremities in the testosterone group compared to placebo. Testosterone was also associated with increased lean body mass. Biochemical results, including testosterone levels, are not yet available.

HIV Pathogenesis

Dr. Deeks dedicated the third and final portion of his remarks to HIV pathogenesis, in particular the “chaos in the gut” caused by HIV infection, a topic of great interest to him. Relatively recent research (Brenchley, 2004) has demonstrated that there is a rapid, dramatic depletion of CD4+ memory T cells in the gastrointestinal tract during acute infection, without evidence of increased activation or turnover. Baker et al. obtained ileal biopsies and compared CD4+ cell counts in the lamina propria of the gut with those in peripheral blood. They found that, while CD4+ cell counts in peripheral blood are quickly normalized with the initiation of antiretroviral therapy, the drugs do not restore intestinal memory T cells. HIV infection persists in the

gut and causes ongoing CD4+ cell depletion there. So what is the impact of HIV on the gut? One hypothesis, said Dr. Deeks, is that the loss of mucosal integrity during acute infection leads to chronic exposure to bowel flora, which in turn leads to chronic local CD4+ T cell activation. As a result of this ongoing distribution of susceptible T cells to the gut, there is ongoing HIV-mediated T cell loss.

Interestingly, massive CD4+ T cell depletion in the gut has no pathogenic consequences in sooty mangabeys, which are natural hosts for SIV. Gordon et al. presented data showing that, despite high levels of viremia and rapid, ongoing depletion of T cells in the gut during acute SIV infection, T cell activation is minimal; further, sooty mangabeys do not experience T cell loss in peripheral blood. Likewise, Pandrea et al., examining African green monkeys (also natural hosts), noted a slight decrease in T cells in peripheral blood during acute SIV infection, with a return to normal levels during chronic infection. CD4+ T cell depletion in the gut was, again, severe and durable but not associated with significant pathogenic consequences. The absence of immune activation in SIV-infected natural hosts suggests that progression of HIV disease may depend on both depletion of mucosal CD4+ T cells *and* significantly increased T cell activation.

MRSA Bacteremia

Dr. Follansbee returned with a report on methicillin-resistant staphylococcus aureus (MRSA) and HIV. MRSA incidence is known to be increasing among the general population. Burkey et al. presented data describing the incidence of MRSA bacteremia in the HIV-infected population. Investigators collected data from 2000 to

2003 from 3554 HIV-infected patients, for a total 8280 person-years, at a large Baltimore clinic. There were 158 episodes of *S. aureus* bacteremia identified (19.1 events/1000 person-years); 60 of these cases were MRSA infections (7.2 events/1000 person-years). The proportion of MRSA incidence was found to have risen from 23.8% in 2000 to 46.7% in 2003. For each case of MRSA infection, 4 non-MRSA controls were randomly selected. In case-control analysis, the factors associated with MRSA bacteremia were injection drug use, end-stage renal disease, HIV RNA levels >400 copies/mL, and CD4+ cell counts <200 cells/mm³. Age, race, sex, use of prophylaxis for opportunistic infections, and concomitant diabetes were not identified as risk factors.

HIV Prevention

Dr. Follansbee concluded by mentioning two presentations on prevention. Rabaud et al. evaluated 4 regimens for post-exposure prophylaxis (PEP) in France, where the standard of care for PEP is a PI + 2 nRTIs for 28 days. The team compared the tolerability of the following combinations, each evaluated in successive PEP studies: (1) Combivir + nelfinavir twice a day (n=401), (2) Combivir + Kaletra twice a day (n=169), (3) Combivir + tenofovir twice a day (n=17), and (4) tenofovir + 3TC + ritonavir-boosted atazanavir once a day (n=152). The rate of discontinuation due to adverse effects was significantly higher in the Combivir + nelfinavir study when compared to any of the other three studies. There was no significant difference among the other three regimens. Because Combivir + tenofovir is not a proven antiretroviral regimen, and because the tenofovir + 3TC +

ATV/r combination is the most expensive of those studied, the authors concluded that Combivir + Kaletra should be the standard PEP regimen.

Finally, Michelle Roland et al. examined the relative benefit of “standard” (2 sessions) vs. “enhanced” (5 sessions) risk reduction counseling in the context of PEP. Persons treated with PEP following sexual exposure were randomized to standard (2 session) vs enhanced (5 session) counseling. The groups were compared for differences in (1) change in number of unprotected sex acts 6 to 12 months post-PEP compared to 6 months pre-PEP; (2) 12 month incidence of further PEP use (re-PEP); and (3) 12 month incidence of HIV acquisition. At 12 months there were reductions in both groups in the number of unprotected sex acts compared to baseline (mean 1.8 and 2.3 fewer acts in the standard and enhanced groups, respectively). Among those with ≤ 4 baseline acts (lower risk), the enhanced group had a slight increase (mean +1.6 acts) compared to the standard group. Among those with >4 baseline acts (higher risk), however, the enhanced group had a mean of 6.2 fewer acts than the standard group. Likewise, differences in re-PEP and HIV acquisition did not differ significantly between counseling groups among those with lower risk, while among higher risk participants enhanced counseling proved significantly more beneficial. The conclusion was that enhanced counseling should be targeted to individuals who report higher baseline risk.

Oral insulin sensitizing agents: thiazolidinediones and metformin

Dr. Mulligan began her final remarks with a summary of previously published information regarding insulin sensitizing drugs and their effects on visceral and subcutaneous fat. One class of these agents is the thiazolidinediones – troglitazone, rosiglitazone, and pioglitazone - which increase peripheral insulin sensitivity. In four studies of HIV-negative patients with lipodystrophy and/or diabetes, troglitazone decreased visceral fat and increased subcutaneous fat; however, the drug was withdrawn from the market in 2001 after it was shown to cause hepatocellular injury. Among patients with HIV infection and lipoatrophy, two studies of rosiglitazone have shown no effect on either visceral or subcutaneous fat, while three other studies indicated that it increased subcutaneous fat; pioglitazone increased subcutaneous fat in one study. Another drug, metformin, which works by decreasing hepatic glucose output, has been shown, in HIV-infected patients, to decrease visceral and subcutaneous fat, total fat, waist circumference, and weight.

Dr. Mulligan then described her own results from ACTG 5082, which she presented at CROI. This study randomized 105 subjects with elevated waist/hip ratio and hyperinsulinemia to one of four study arms: (1) metformin 1000 mg BID + rosiglitazone placebo (n=26), (2) rosiglitazone 4 mg daily + metformin placebo (n=27), (3) metformin 1000 mg BID + rosiglitazone 4 mg daily (n=25), and (4) metformin placebo + rosiglitazone placebo (n=27). Patients underwent abdominal visceral and subcutaneous adipose tissue measurement by CT, as well as determination of whole body and regional fat distribution by DEXA. All three treatment groups experienced

improvements in insulin sensitivity, but visceral fat was not affected. Leg fat increased with rosiglitazone but not with metformin. Metformin tended to decrease subcutaneous fat while rosiglitazone tended to increase it, and the combination effected no change; however, these results did not achieve statistical significance. Rosiglitazone alone increased LDL cholesterol and decreased HDL cholesterol, but no such effect was noted in either metformin treatment group. However, there was a high dropout rate in the metformin-alone group, associated with diarrhea and mild lactate elevations.

Another study of metformin for visceral obesity was conducted at Tufts (Kohli et al.), among HIV-positive individuals with increased abdominal girth but *without* insulin sensitivity impairment. Patients were given metformin 1500 mg or placebo daily for 24 weeks and their visceral fat was measured by DEXA. There was no significant change detected in visceral fat after 24 weeks; lipids and glucose, insulin, and insulin AUC were likewise unaffected. However, limb fat and body mass index (BMI) decreased significantly. The authors thus concluded that there is no evidence to support the use of metformin in patients with lipodystrophy but normal glucose tolerance.

Finally, a French trial, presented by Slama et al., evaluated the effect of pioglitazone on HIV-associated lipoatrophy in 130 HIV-positive patients, also normoinsulinemic, taking antiretroviral therapy. Patients took pioglitazone 30 mg daily for 48 weeks. The study’s primary endpoint was change in limb fat, as measured by DEXA, from week 0 to week 48, and there was a modest but statistically

significant mean increase with pioglitazone (380 g) compared to placebo (50 g). Among patients who were not receiving concomitant d4T, there was a more pronounced difference (400 g) between those on pioglitazone and those on placebo. In patients taking d4T the difference was not significant. Pioglitazone had no effect on visceral or subcutaneous abdominal fat and, despite the slight change in limb fat, patients perceived no improvement in lipodystrophy. Glucose, insulin, LDL cholesterol, and triglycerides were unaffected, though HDL cholesterol increased slightly.

So, concluded Dr. Mulligan, whither thiazolidinediones in HIV lipodystrophy? They seem to have no effect on visceral fat, and their effects on subcutaneous fat are inconsistent. Where changes in subcutaneous fat do occur, they are generally modest and not detectable to the patient. Patients who are not taking thymidine analogs, such as d4T, are more likely to benefit. Rosiglitazone adversely affects lipids, while pioglitazone does not. Pioglitazone, though, is partly metabolized through the CYP3A4 pathway, and its potential pharmacokinetic interactions are yet unknown; rosiglitazone may therefore be the favored option until PK results are available.

Finally, Dr. Mulligan noted that there are ongoing open-label studies of novel metabolic agents at SFGH: (1) IGF-I/IGFBP-3 in patients with excess visceral fat and insulin resistance, and (2) leptin in patients with elevated triglycerides and low leptin levels. Those desiring more

information were referred to Viva Tai, at (415) 206-4090.

These remarks concluded the *Report Back from CROI*. Dr. Abrams thanked the speakers, as well as the following organizations that made the evening possible through their generous unrestricted educational grants: Bioscrip Pharmacy, Gilead, Merck, Roche, Virco Lab and ViroLogic.

2006 membership renewal

We once again seek your support to assist us in the work that we do for HIV care providers in the Bay Area and beyond. We appreciate that there are many competing demands and requests for our ever shrinking resources, but we hope you will renew your Consortium membership to help us accomplish our goals and better serve your needs. We need to keep an accurate updated list of individuals interested in learning of Community Consortium activities, following our research endeavors, and gleaning whatever gossipy tidbits *Synopsis* may otherwise have to offer. To this end, we ask for you to send back the enclosed membership application with the nominal fee that helps us with the printing and mailing of *Synopsis* and some of our other educational brochure materials. In addition, we have always claimed that our strength is in our numbers. When the Consortium takes a stance on an issue and, for example, writes a letter to an elected official, it behooves us to say that we are an organization of X plus HIV care providers in the San Francisco Bay Area. Obviously, the larger the X number that fills in the blank, the more

clout we have. The Community Consortium has much to be proud of. We serve as an ongoing model for community based clinical trials and provider education throughout the country. We know there are more providers out there who would be interested in our programs, so feel free to copy your form and share with colleagues! Thanks again for your continued support!

Clinical Trials Update

SMART (CPCRA 065)

Strategies for Management of AntiRetroviral Therapy, halted enrollment in early January 2006 just short of reaching the intended accrual of 6,000 participants. As of January 11, 2006, when enrollment was stopped, 5,472 volunteers had joined the study, 112 at the Community Consortium.

Follow-up visits will continue for all participants in the SMART trial while the study team considers plans for study modification and longer follow-up. The investigators will analyze the SMART study data in detail to gain insights into the reasons for the unanticipated increased risk of HIV disease progression, death and treatment related complications in the DC arm compared to the VS arm which led to early termination of enrollment.

Please refer to the 'Report Back from CROI' SMART section on page 11 for more details. For further information visit the SMART Study website at: <http://www.smart-trial.org/>

Anal Dysplasia (SMART Substudy CPCRA 065F)

The SMART Protocol Team closed the Anal Dysplasia study on March 16, 2006. As SMART enrollment closed, no new participants could be accrued into this substudy. As of its closing date, 30 patients had been enrolled and 29 others had consented and were being screened for the substudy prior to randomization into SMART. High-grade dysplasia, which was an exclusion for participation as it was a study endpoint, was confirmed by anal biopsy in 8 of the 59 total patients (13.6%). The substudy team believes that, while small, the data set can be assembled for publication as a cross-sectional description of the prevalence of anal dysplasia and HPV infection .

Neurology (SMART Substudy CPCRA 065G)

This substudy of SMART opened to accrual in late 2005. Enrollment was tied to new participants in SMART only. As enrollment into SMART has closed, no new enrollments into Neurology can take place. We are awaiting a decision on the ultimate status of the Neurology substudy.

Opioids and Cannabinoids Pharmacokinetic Interactions

Funded by NIDA, this new study's primary objective is to assess whether smoking cannabis affects the pharmacokinetics and metabolism of widely used opioid

analgesics in patients with cancer. The study proposes to do this by investigating the effects of vaporized cannabis in patients prescribed morphine or oxycodone for cancer-related pain. It will also assess the clinical safety of the concomitant use of cannabinoids and these opioids by monitoring the short-term side effects associated with combined therapy.

Chronic pain conditions remain problematic, especially in patients with cancer. Although opioids are effective analgesics, dose-limiting side effects in the form of sedation, nausea and vomiting, and fear of dependence often limit their use at higher – and possibly more effective – doses. Of particular interest, however, is the potential for greater than additive analgesic effect of cannabinoids and opioids in combination that would allow for opioid analgesic effect to be achieved at *lower* dosages than are necessary alone, which could overcome problems with both tolerance and side effects for both drug classes. Unfortunately, safety data on the combination in humans does not exist at this time and needs to be obtained. As increasing numbers of patients with cancer may turn to cannabis to augment the effects of their opioid analgesics, data on potential pharmacokinetic interactions and clinical safety of the combinations should be evaluated in a controlled clinical research setting. If you have patients with cancer on the eligible pain regimens who might be interested in this 3 night SFGH inpatient General Clinical Research Center-based study, please have them contact Hector Vizoso, at (415) 476-9554, ext. 366.

Genomics (CPCRA 066)

We have currently enrolled 101 patients into the Genomics study (CPCRA 066). The study obtains a whole blood sample to archive for use in future studies investigating associations between human

genetic factors and clinical data collected in qualifying CPCRA studies for the purpose of addressing questions related to HIV-infection or conditions relevant to the health of persons with HIV infection. HIV-related questions may be related to the epidemiology, diagnosis, pathogenesis, complications, treatment, and prognosis of HIV-infection. Examples of conditions relevant to the health of persons with HIV-infection include, but are not limited to, hepatitis C, Kaposi's sarcoma, and disorders of lipid metabolism. To qualify for this study, participants must be enrolled in a qualifying CPCRA study.

ESPRIT

Enrollment into ESPRIT (The Evaluation of Subcutaneous Proleukin in a Randomized International Trial) closed on May 30, 2003, with 4150 participants randomized in this 25-nation international trial. The Community Consortium enrolled 42 of the target goal of 50 subjects, with the majority coming from our Emory University "satellite" site in Atlanta. The current focus of the study is to maintain participants in follow-up and to make sure that those individuals randomized to the IL-2 intervention continue to receive cycles of therapy to maintain their CD4+ cell counts at the target level.

The DSMB last met in February 2006 and found no concerns that would affect the study. You can read the DSMB summary on our website at: http://communityconsortium.org/research/dsmbmemo_feb2006.pdf

FIRST (CPCRA 058)

The CPCRA's Flexible Initial Retroviral Suppressive Therapies (FIRST) trial closed on September 16, 2005. An

Executive Summary Report was released February 3, 2006. You can view the report at http://communityconsortium.org/research/FIRST_exec_summary_final2.pdf

LTM (CPCRA 060)

The final group of patients who are being followed in the CPCRA 060 naïve cohort will complete follow-up on July 1, 2006. In order to have the most complete information on the patients in the naïve cohort at the end of the study, all LTM Naïve Cohort study participants will have blood drawn for plasma storage and as centrally processed viral load between January 1, 2006 and July 1, 2006. To date, 3,180 patients are being followed on LTM nationwide, including 173 from our site.

Oyster Mushrooms

To date, 18 subjects have completed our 8-week, pilot study of oyster mushrooms for treatment of antiretroviral-induced hyperlipidemia in HIV-infected patients. Only two more participants are needed! The study is open to individuals who have been taking either efavirenz or a ritonavir-boosted PI for at least 12 weeks and who have non-HDL cholesterol levels 160 mg/dL or higher. Those currently using cholesterol-lowering agents, or who have a history of abnormal muscle conditions caused by such treatments, are excluded. Once enrolled, patients are followed at the General Clinical Research Center (GCRC) at San Francisco General Hospital, with two overnight inpatient visits and three

outpatient visits over the course of the study. Participants can receive up to \$300 in compensation. If you have patients who might be interested in this study, please have them contact Paul Couey, at (415) 476-9554, ext. 315.

The Staying Well Study: A Clinical Trial of Meditation or Education Groups for HIV Infection

Is there anything that can be done to slow the loss of CD4+ T-cells other than starting anti-retrovirals? That is one of the key questions being addressed by the Staying Well Study. Observational data shows that stress and depression are both associated with more rapid loss of CD4+ T-cells.

Little is known about whether interventions that address stress and mood are capable of slowing the loss of CD4+ T-cells, however.

The Staying Well Study is a randomized, controlled clinical trial to compare the impact of Mindfulness-Based Stress Reduction (MBSR), a meditation-based program that is taught in eight weekly sessions, to HIV education/support groups. MBSR has been shown to improve perceived stress and improve mood in prior trials. In addition to assessing the impact of the intervention on CD4+ T-lymphocyte cell counts and HIV RNA levels, the study aims to assess whether MBSR improves quality of life and mood in the study participants. The study will also perform detailed assessments of the intervention on stress hormones, and test specific mechanisms through which stress and mood may alter HIV-related immune function.

Dr. Susan Folkman and Dr. Rick Hecht at the UCSF Osher Center for Integrative Medicine are leading the study, with about a dozen other UCSF researchers and funding from the National Institutes of

Health. Participants will be followed for one year. The study eligibility criteria include currently being off antiretrovirals (prior treatment is OK if it has been stopped at least 4 months), a CD4 T-lymphocyte count > 250 cells/ μ m, and a viral load > 3000 copies/ml. The education/support groups will be led by Project Inform and are designed to be as useful and interesting as possible for participants. After one year, participants randomized to the education/support groups will be able to take the MBSR course for free. For more information about the study, please contact Patty Moran, PhD, at (415) 353-9745 or moranp@ocim.ucsf.edu, or call the study information number: (415) 353-9744.

Other Studies

The ACE Study

The HIV Research Section of the San Francisco Department of Public Health's AIDS Office is conducting the ACE study to test whether suppressing genital herpes outbreaks using acyclovir, a safe and well-tolerated herpes therapy, will prevent men who have sex with men from contracting HIV. Genital herpes, caused by the virus HSV-2, is one of the most common sexually transmitted diseases - about 25% of all sexually active adults in the United States are infected with the virus, though as many as 80% of them are not aware of their infection. Furthermore, studies show that HSV-2 infected people may be twice as likely to acquire HIV if they are exposed. Participants in the ACE study will take acyclovir or a placebo daily for one year. Any participant who experiences a herpes outbreak during the year will be treated with open label

acyclovir. Participants will receive free herpes screening, HIV testing, risk reduction and adherence counseling, and compensation for their time. If you are interested in finding out more information about the study, please contact the Research Section at (415) 437-4782 (HSV2), or visit the website at www.sfajdsresearch.org.

Organ Transplants

The "Solid Organ Transplantation in HIV: Multi-Site Study", is a study to evaluate the safety and effectiveness of kidney and liver transplants in a select population of HIV infected individuals. This study is supported by the National Institute of Allergy and Infectious Diseases and sponsored by the University of California, San Francisco. To be eligible, subjects must meet criteria for transplantation, have a T-cell count > 200 (kidney) or > 100 (liver) cells/mm³, and meet HIV viral load criteria depending on which organ is needed. Patients with certain opportunistic infections in the past will be considered at some centers.

Complete study information can be found at: <http://hivtransplant.com/>.

Project T: Tenofovir Pre-Exposure Prophylaxis

Project T is a CDC-sponsored safety study of antiretroviral medication as pre-exposure prophylaxis (PrEP) in HIV-negative men who have sex with men (MSM). The study's rationale is that antiretroviral medication could complement existing behavioral methods to prevent HIV infection, and this

approach may be useful for HIV-negative individuals at intermittent or persistent high risk.

Tenofovir is a promising candidate for PrEP. It has a favorable pharmacologic profile, including low incidence of side effects, once daily dosing and slow development of resistance. There are, as well, encouraging non-human primate data: several studies of pre- and post-exposure TDF in macaque monkeys (Tsai et al. and Van Rompay et al.) have indicated that it may be able to prevent SIV infection. Efficacy in these studies ranged from 50% to 100%, depending on dose, timing and duration of TDF.

There are currently several phase II/III international safety and efficacy trials of tenofovir PrEP either planned or underway. To complement these international trials, the CDC developed a US trial in men who have sex with men (MSM).

The study is designed as a randomized, double-blind, placebo-controlled, phase II extended safety trial, conducted at two sites (San Francisco and Atlanta). Two hundred MSM will be given TDF 300 mg qd or placebo for 24 months. The primary endpoints are clinical safety/tolerability and sexual risk behavior; secondary endpoints are resistance patterns in seroconverters, adherence and social harms. The study is not powered to determine efficacy.

Subjects are randomly assigned 1:1:1:1 to the following cohorts: (1) TDF for the duration of the study ($n = 100$), (2) placebo for the duration of the study ($n = 100$), (3) no pills for 9 months, then TDF for the remainder of the study ($n = 100$), and (4) no pills for 9 months, then placebo for the remainder of the study ($n = 100$). The intention of this schema is to determine

whether simply taking a pill affects sexual risk behavior. Study visits over the 2 years will include rapid HIV/STD testing and safety labs every three months; DEXA scans yearly; and risk behavior and adherence measures and risk reduction counseling at each visit. Subjects may request HIV/STD testing at any time between visits. Seroconverters will stop therapy and be followed for another year.

For further information, or to refer participants, call Dr. Albert Liu at (415) 554-9104.

Magnetic Resonance Imaging and Spectroscopy of the Brain in HIV

To characterize events in the central nervous system (CNS) in HIV-infected individuals, investigators at SFGH and the SFVAMC are seeking patients with HIV to participate in research using magnetic resonance imaging and spectroscopy (MRI/MRS) of the brain. This protocol focuses on subjects who are initiating or interrupting antiretroviral therapy under the supervision of their providers either independently or as part of a protocol such as SMART. The rationale for this study is that MRS allows detection of cerebral metabolites which reflect inflammation, gliosis, neuronal injury, and repair. The study team hypothesize that the changes in plasma and CSF viral load induced by alterations in HIV-1 treatment status will induce immune and metabolic changes in the brain that will be detectable on MRS imaging. Participation in this study will also involve phlebotomy, brief neuropsychological testing, and lumbar puncture performed by one of two neurologists (Drs. Serena Spudich or Richard Price).

The investigators will examine subjects at several serial time points after starting or stopping therapy. Detailed screening for exclusion criteria (including presence of ferromagnetic objects such as pacemakers, contraindication for lumbar puncture such as bleeding diathesis, and pregnancy) will be performed by study staff at the time of referral. Participants will receive up to \$495 in compensation.

For further information or to refer participants for the study, please contact the study coordinator, Nicole Lollo, at (415) 206-4328, or Dr. Spudich at (415) 206-4487, sspudich@itsa.ucsf.edu.

Pilot Study of the Effect of Minocycline on CSF HIV-1 Infection

Dr. Richard Price of the Department of Neurology and colleagues at UCSF/SFGH are conducting a NIH funded study looking at the effectiveness of minocycline for treating HIV infection of the nervous system. Eligible participants will undergo 5 blood draws and 4 lumbar punctures over a period of 14 weeks; medication (minocycline) will be provided. Inclusion criteria include: adult (at least 18 years of age), documented HIV infection, not on antiretroviral therapy (naïve or off therapy at least 6 weeks prior to enrollment). Exclusion criteria include: females who are pregnant or expectation of pregnancy during the study, taking a tetracycline in the past 6 months prior to enrollment. If you have patients who may qualify for this study and are interested in

being screened, please have them contact the Study Coordinator, Nicole Lollo, at 415-206-4328.

looking for an IRB?

The Project Inform Institutional Review Board was established in 1989 to oversee local community-based clinical trials – studies conducted at sites other than those affiliated with UCSF, Kaiser Permanente, or, in the East Bay, Alta Bates Medical Center. The IRB’s mission is to protect the participants in these trials by determining whether the study protocol and ongoing protocol-related activities are clinically and ethically sound and compliant with applicable regulatory requirements. Project Inform sites contribute the bulk of the Community Consortium’s study referrals; hence, the IRB has reviewed a large number of studies conducted by the Consortium, from the early OI treatment and prophylaxis trials to the current Anal Dysplasia and Neurology substudies in the SMART protocol. The Board does not, however, limit its review to Consortium research activities. Since its inception, it has provided initial and ongoing review for over 80 studies and study proposals submitted by providers from both the Consortium and the wider Bay Area medical community. The IRB, along with the sponsoring institution, Project Inform, continues to encourage and support HIV clinical research ideas that stem from the local non-academic setting.

Chaired by Dr. Stephen Follansbee and composed entirely of volunteers, the Project Inform IRB offers its review services free of charge to all community investigators. If you are interested in submitting a study protocol for review, you

may contact Paul Couey, the IRB Coordinator, at (415) 476-9554, ext. 315.



**Are you HIV+
and feeling stressed,
but not taking meds?**

**Free meditation-based stress management or
education sessions!**

**We are seeking HIV+ participants for a UCSF research study on the
effects of meditation-based stress management and education on
physical health and well-being.**

To participate you must be:

- **at least 18 years old**
- **not currently on antiretroviral medication**

**Participants will be compensated \$25 plus parking/transportation costs for each
of the four study visits.**

**Please call us to find out more: (415) 353-9744
www.osher.ucsf.edu/stayingwell**