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upcoming conferences

45TH INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY (ICAAC)

December 16-19, 2005
Washington, DC
<http://www.icaac.org/>

THE 13TH CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS (CROI)

February 5-9, 2006
Denver, CO
<http://www.retroconference.org/2006>

THE 16TH INTERNATIONAL AIDS CONFERENCE (IAC)

August 13-18, 2006
Toronto, Canada
<http://www.aids2006.org/>

employment opportunities

HIV Experienced Physician Sought

To join primary care practice at 45 Castro Street. Associate sought for clinical and hospital practice.

Contact Stephen Knox, M.D., at 415-863-3366.

HIV Clinical Research Nurse and Mid-level Practitioner Positions Open

The HIV Research Section of the San Francisco Department of Public Health is hiring a research nurse and mid-level practitioner (NP or PA). Hours: part-time to full-time available. Duties include interviewing study participants; conducting informed consent; performing histories and physicals,

phlebotomy, HIV testing and counseling, adherence counseling, and quality control procedures; dispensing medication and administering vaccines; assisting with research protocol development and implementation. Mid-level practitioner will also oversee the specimen collection and processing program and supervise a full time lab assistant. Studies include HIV vaccine and other HIV prevention intervention trials. Experience in HIV clinical research with a culturally diverse population desired. Please email CV to research.jobs@sfdph.org or mail to HIV Research Hiring Official, 25 Van Ness, Suite 500, San Francisco, CA 94102.

congrats dr. dan!

The Community Consortium would like to recognize Dr. Daniel Wlodarczyk, for winning the Jefferson Award in June for his outstanding work in the community. In 1972, Jacqueline Kennedy Onassis, U.S. Senator Robert Taft, Jr., and Sam Beard founded the American Institute for Public Service, a 501c3 public foundation, to establish a Nobel Prize for public and community service - The Jefferson Awards. The Jefferson Awards are presented on two levels: national and local. On the local level, Jefferson Awards recipients are ordinary people who do extraordinary things without expectation of recognition or reward.

For the last 15 years, Dan has been a volunteer at Street Outreach Services, a mobile medical unit that provides basic care, clothes, and hygiene supplies to San Francisco's homeless. For the last 20 years, Dr. Dan has divided his time between Bayview and San Francisco General Hospital. All these years later, he's still working six days a week on the AIDS

ward, helping thousands of people who come here take the cocktails of medications needed to keep them stay alive.

For his tireless efforts to bring quality health care to the under-served and his humanity and inspiration in the fight against AIDS, Dan wins the Jefferson Award in the Bay Area!!

new hiv grand rounds

San Francisco General Hospital's Division of HIV/AIDS is pleased to announce the commencement of HIV/AIDS Grand Rounds. This CME accredited series highlights the latest diagnostic, research and treatment information regarding the pathogenesis and management of HIV disease. Presentations include clinical case conferences, report-backs from important HIV meetings, updates on current HIV research, and subspecialty reviews of the optimal management of particular aspects of HIV disease.

The lecture series is held in Carr Auditorium, Building 3, on the San Francisco General campus, every Wednesday from 8 to 9 AM and is open to both SFGH and community providers. Light refreshments are served. This activity has been approved for a maximum of 1 category one credit toward the AMA Physician's Recognition award. For any questions about HIV/AIDS Grand Rounds, please contact the coordinator, Annie Luetkemeyer at aluetkemeyer@php.ucsf.edu

Happy Holidays!



Donald I. Abrams, M.D.,
Editor



Paul Couey
Guest writer

On August 17, 2005, the Community Consortium hosted a *Report Back from the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment*, at Genentech Hall, on the UCSF Mission Bay campus. Steve O'Brien, MD, Director of the East Bay AIDS Clinic, moderated the event, and the guest speakers were William Owen, MD, private practice, California Pacific Medical Center - Davies Campus, Diane Havlir, MD, Director of the UCSF Positive Health Program, and C. Bradley Hare, MD, also of the Positive Health Program. The IAS Conference occurs biannually, alternating with the International AIDS Conference, and this year was held July 24-27 in Rio de Janeiro, Brazil.

Novel Antiretroviral Agents

Dr. Owen began the discussion by covering a number of presentations on new NRTIs, NNRTIs, PIs and entry inhibitors that are at various stages of development. There are many agents in the pipeline, and Dr. Owen chose to focus on representative agents from each category that were of particular interest to him.

Cal Cohen presented data on virologic response to D-d4FC, the nucleoside analog otherwise known as Reverset, from a dose-ranging study in treatment-experienced patients. Preclinical data showed activity against mutant viral strains resistant to 3TC, AZT, and tenofovir (TDF), as well as other NRTIs, NNRTIs and PIs. In addition, 10-day add-on dosing demonstrated viral load decreases of 0.8 \log_{10} in treatment-experienced patients taking the 200 mg dose (versus 1.8 \log_{10} at the same dose in those naive to therapy). The RVT-203 study randomly assigned 199 patients, viremic on their baseline regimens (viral loads >2000 copies/mL), to 4 dosing groups: 50, 100 and 200 mg and placebo. Patients underwent a 2-week add-on phase, followed by 14 weeks with an optimized background regimen, and an additional 8-week placebo crossover. Virologic response (viral load decrease

$>1.0 \log_{10}$) was achieved by 54% of patients taking the 200-mg dose of D-d4FC, compared to 38% at 50 mg, 31% at 100 mg, and 40% in the placebo group. However, at all doses there are limitations on the use of D-d4FC with other NRTIs. In the patients taking D-d4FC with either FTC or 3TC, the mean \log_{10} viral load decrease at 2 weeks was less than half of those achieved by patients *not* on FTC or 3TC. Also, there was an increased incidence of hyperlipasemia among patients D-d4FC and ddI; there were 3 cases of symptomatic pancreatitis, all in the 100 mg D-d4FC group.

Steve Becker et al. reported on a novel non-nucleoside agent, GW695634, with significant antiviral activity against NNRTI-resistant virus. In the 7-day add-on study described, 27 of the 44 NNRTI-experienced patients enrolled had at least one NNRTI mutation at baseline; the remaining 17 had a history of such mutations. The most common mutations were K103N, V108I and Y181C. At baseline, median viral loads were 4.4 – 4.6 \log_{10} and CD4+ cell counts were 230 – 345 cells/mm³. Participants were randomized in double-blinded fashion to receive placebo or one of 4 doses of GW695634: 100 mg, 200 mg, 300 mg or 400 mg twice daily. Seven days of

treatment with GW695634 yielded, across dosing groups, median viral load reductions of 1.1 – 1.6 log₁₀, compared to a 0.14 log₁₀ increase in the placebo arm. The most common side effects were diarrhea, nausea and rash, all mild to moderate.

There were several presentations on TMC 114, a protease inhibitor that is becoming familiar to San Francisco providers. Katlama et al. reported on the planned 24-week interim analysis of POWER 1, an ongoing European study of TMC 114 boosted by ritonavir in patients with triple-class experience and at least one primary PI mutation. Patients were randomized to receive either an investigator-selected control PI (n = 63) or TMC 114/r at one of the following doses: 400/100 mg (n = 64) once daily, 800/100 mg (n = 63) once daily, 400/100 mg (n = 63) twice daily, or 600/100 mg (n = 65) twice daily. An optimized background regimen was chosen at baseline. The highest TMC 114/r dose regimen proved most effective virologically, significantly more so than the comparator PIs: 77% of those in the 600/100 mg BID arm achieved ≥ 1.0 log₁₀ viral load reductions, versus 29% in the comparator arm. Additionally, subgroup analyses of those receiving TMC 114/r 600/100 mg BID showed significant benefit versus comparator PI (in percentage reaching viral loads <50 copies/mL) for patients who did or did not use T-20 concomitantly, those who had 3 or more primary PI mutations, and those for whom baseline genotype predicted no sensitivity to any background antiretroviral agents. The rate of adverse events for the

600/100 mg BID dose was found to be comparable to that of the comparator PI arm (Grinsztejn et al.). The most common toxicities were headache and gastrointestinal disturbance. Finally, a pharmacokinetic study (Sekar et al.), separate from POWER 1, found no interaction between TMC 114 and either omeprazole 20 mg or ranitidine 150 mg BID.

Moving on to CCR5 inhibitors, Dr. Owen reported that there are three such agents in development: maraviroc (Pfizer), aplaviroc (GlaxoSmithKline) and vicriviroc (Schering Plough). Presentations at IAS showed marked declines in viral load (1.5 log₁₀ or higher) for each of these drugs. Phase II and III trials are underway. [*Note: GSK halted all trials of aplaviroc for naive pts on 9/15/05, due to hepatotoxicity concerns. Phase II trials continue in treatment-experienced patients, with closer monitoring.*] It is notable that, in pharmacokinetic assays, vicriviroc vastly increased the C_{max} and AUC of ritonavir and ritonavir-containing regimens (Saltzman et al.).

Finally, Dr. Owen touched on oral fusion inhibitors in the drug development pipeline. Very preliminary work has begun in the search for alternatives to T-20, which is currently the only FDA-approved HIV-1 entry inhibitor. As with most peptides, T-20 is not orally available; additionally, it is quite expensive. Jiang et al. presented data on NB-2 and NB-64, small-molecule compounds with potent inhibitory activity against gp41-mediated membrane fusion. These agents have demonstrated antiviral activity against a range of HIV-1 isolates, including R5, X4, and R5/X4 biotypes as well as genotypic clades A through G and group O. The study team has identified 20 similar compounds with stronger activity,

signaling the imminent emergence of orally available, less expensive fusion inhibitors as a powerful antiretroviral option.

First-Line Regimens: Activity/Tolerance/Resistance

Dr. Havlir spoke next, prefacing her remarks with the announcement that the Positive Health Program would be instituting weekly Grand Rounds, beginning September 21. She encouraged community care providers to attend.

There were three conference presentations of interest to Dr. Havlir regarding first-line antiretroviral regimens. Pozniak et al. reported on results of the Gilead 934 trial, a comparison of once-daily efavirenz + FTC/TDF versus efavirenz once daily + AZT/3TC twice daily in 509 antiretroviral-naïve patients with viral loads >10,000 copies/mL. Combivir was used in the study but Truvada, the fixed dose combination of FTC and TDF, was not used. ITT analysis at 48 weeks showed FTC/TDF outperforming CBV both in proportion of subjects achieving viral loads <400 copies/mL (81% vs. 70%) and in mean CD4+ cell count change from baseline (+190 vs. +158 cells/mm³). Additionally, there was less increase in fasting total cholesterol in the FTC/TDF arm: 21 mg/dL vs. 35 mg/dL, a statistically significant difference. Week 48 genotyping showed a low rate of resistance mutations for both arms, though CBV was slightly higher for both efavirenz mutations and M184V/I. There was related information from this study that strongly supports the idea that baseline genotyping should be done before patients are prescribed

antiretroviral therapy. Of the 509 patients in the trial, 22 had baseline NNRTI resistance while 13 had NRTI resistance. The NNRTI mutations were associated with poor virologic response: 2 of those 22 subjects achieved viral loads <400 copies/mL at week 48. NRTI resistance, conversely, had little impact: 12 of 13 reached <400 copies/mL. This is not surprising information, said Dr. Havlir, but it is highly relevant for local providers, who see substantial numbers of antiretroviral-naïve patients with resistant virus.

The second presentation (Molina et al.) dealt with Abbott's Study 418, which compared once versus twice daily Kaletra (LPV/r) dosing at 96 weeks. This open-label study, conducted in antiretroviral-naïve subjects with viral loads >1,000 copies/mL and any CD4+ cell count, randomized participants 3:2 to LPV/r 800/200 mg QD (n = 115) or LPV/r 400/100 mg BID (n = 75). The accompanying NRTIs for both arms were TDF and FTC. At 96 weeks, 91% of subjects on the BID arm had reached HIV RNA levels <50 copies/mL, compared to 89% in the QD arm (observed data, not ITT analysis). The study thus demonstrates equivalent efficacy; however, there was a significant difference between arms in the rate of grade 3-4 gastrointestinal disturbances (17% in the QD arm versus 5% in the BID arm). The data confirming noninferiority confirm findings presented last year at ICAAC, and once-daily Kaletra dosing is now considered a reasonable option for antiretroviral-

naïve patients, according to US Public Health Service guidelines. It is not recommended for treatment-experienced patients or those taking concomitant NNRTIs.

The final presentation in this category, one with perhaps the greatest import globally, concerned information from the DART study. DART, conducted in Uganda and Zimbabwe, enrolled 3315 previously untreated HIV-infected subjects with CD4+ cell counts <200/mL³ and WHO classification stage 2, 3 or 4, and randomly assigned them to initiate triple antiretroviral therapy with either Clinical and Laboratory Monitoring (not including virology) or Clinical Monitoring Only. Of these subjects, 74% started CBV plus TDF as first-line therapy. Kaleebu et al. presented 48-week data on a subset (n = 300) of these patients who enrolled in a retrospective virology substudy designed to assess virologic response and describe mutations in patients with viral loads >1000 copies/mL. Results at 24 weeks were reported at CROI 2005, and the findings were similar at 48 weeks: there was a 4.1 log₁₀ mean decrease in HIV RNA copies/mL, along with a mean increase in CD4+ cell count of 126 cells/mm³. By intent-to-treat analysis, 65% of subjects achieved viral loads <400 copies/mL and 55% reached <50 copies/mL. Some of those attending the conference interpreted these results as good and some were less sanguine, said Dr. Havlir; however, she opined, given the limited treatment options in this resource-constrained setting, these data are at the very least intriguing. Some potential advantages of the regimen in such areas are that (1) none of the agents require refrigeration, (2) there is no nevirapine-hypersensitivity risk, (3) there are no rifampin interactions and (4) pregnant women can safely use these drugs. This 4th

attribute is particularly relevant: 66% of participants in this substudy were women.

The DART substudy also produced information on the development of resistance on this regimen. In the 48 patients with viral loads >1000 copies/mL at week 48, there were 20 that were evaluable for genotyping. Eighteen had key mutations, and both of the patients without mutations had been off treatment due to pregnancy and adverse events. Four patients had only the M184V mutation and 1 had only thymidine analog mutations (TAMs). Ten had M184V + TAMs. Interestingly, there were 3 cases of K65R mutation, with or without TAMs. Theoretically, AZT's antagonism to TDF along the excision pathway should prevent the development of this mutation, but this was clearly not the case in this small sample.

Switching

Dr. Havlir next summarized several presentations about antiretroviral "switching." First, Gatell et al. reported 24-week results from the SWAN study, an evaluation of the safety and efficacy of switching from a twice-daily and/or ≥3 pills/day PI to atazanavir (n = 253) or, if combined with TDF, ritonavir-boosted atazanavir (n = 25). Participants were virologically suppressed at baseline (HIV RNA <50 copies/mL) on a PI-based regimen, and were randomized 2:1 to either switch to ATV or remain on the same PI. The patients who switched to ATV maintained viral suppression and had more favorable lipid profiles than those who did not switch. Many providers have been making this switch in the clinic, for both regimen

simplification and lipid normalization, and their reasoning is corroborated by these study results.

The 48-week final results of the E-184V study, 3TC monotherapy versus treatment interruption, were presented by Castagna et al. This study enrolled patients on HAART with the M184V mutation, viral loads >1000 copies/mL and CD4+ counts >500 cells/mm³ who were requesting a treatment interruption. The 1:1 randomization scheme assigned 29 patients each to a 3TC monotherapy arm (300 mg daily) and a treatment interruption arm, and the groups were well matched for CD4+ count, viral load, prior AIDS diagnosis and prior antiretroviral use. The protocol-defined endpoint was a CD4+ count <350 cells/mm³ or a CDC category B or C event, which triggered a resumption of HAART. The proportion of patients meeting this definition of failure was 41% in the 3TC arm and 69% in the treatment interruption arm. Change in viral load also favored the 3TC arm. Additionally, 3TC monotherapy was associated with fewer HIV-related adverse events and less recovery of viral replication capacity, and neither arm produced an increase in resistance mutations. The reason for this benefit is unclear, Dr. Havlir said, but 3TC does appear to affect viral fitness and, as reported previously, it has a persistent antiretroviral effect even when its key mutation is present.

There continue to be new data regarding PI maintenance monotherapy. Previous trials

demonstrated a high risk of virologic failure; however, ritonavir-boosted PIs may be feasible for monotherapy, since they have higher potency and less risk of resistance. We know from previous research that patients who “break through” on PI/r regimens continue to show genotypic sensitivity to the PI. Small trials of lopinavir/r and atazanavir/r have shown promising results, which were presented at the conference (Arribas et al., Vernazza et al.). Certainly, the use of maintenance therapy in suppressed patients is an attractive option for long-term treatment. It will be important for clinicians to know the likelihood of success with this strategy in individual patients, Dr. Havlir pointed out, and she noted that laboratory analysis over the next year could make such predictive information available.

Dr. Havlir closed with a brief mention of two presentations regarding the combination of ddI, TDF and EFV. We know, because it has been much discussed, that TDF + ddI is not advised as a backbone regimen for treatment-naïve patients; it drives the virus down the wrong resistance pathway and makes virologic failure much more likely. But what about switching patients who are already on treatment and fully suppressed? The TEDDI study confirms previous reports of virologic failure in antiretroviral-naïve patients receiving EFV + TDF + ddI; those reports prompted the study team to perform an unplanned interim analysis at week 12, and they found a failure rate of 25% (van Lunzen et al.). The EFADITE trial was designed to evaluate switching stably suppressed patients to EFV + TDF + ddI versus continuing them on their current regimens. The trial found that most patients maintained viral suppression; however, those who switched experienced a significant decline in CD4+ cell counts (median change -25 cells/mm³ vs. +46

cells/mm³ in the continuation arm after one year) (Barrios et al.). Hence, incontrovertibly, this is not a regimen for suppressed or treatment-naïve patients.

Treatment Experienced Patients and Resistance

Dr. Hare focused his initial remarks on some of the issues surrounding antiretroviral resistance in treatment-experienced patients. First he discussed data on tipranavir/r from the RESIST-1 and -2 studies. These were the studies that led to TPV's licensure in June 2005, having demonstrated the superior efficacy of TPV/r compared to that of LPV/r, ATV/r, IDV/r and SQV/r. At IAS, Valdez et al. presented some side analyses of data derived from the study patients who were given TPV/r. An evaluation of 400 samples from these patients yielded the relative impact of several factors in TPV/r response. TPV/r alone was associated with a 1.25 log₁₀ decline in viral load at week 24; enfuvirtide (T-20) provided an additional 0.91 log₁₀ drop; and for each active drug in the optimized background regimen, there was another estimated 0.24 log₁₀ drop. A negative factor was the number of mutations at codons 33, 82, 84 and 90: each mutation accounted for a 0.17 log₁₀ increase in viral load. TPV/r is significantly more effective in combination with T-20. An experimental model demonstrated that, in patients who achieve a TPV inhibitory quotient greater than 60 and who are taking T-20, 60% might expect viral loads <400 copies/mL at week 24 and 37% should reach levels <50 copies/mL - remarkable results in a population of highly treatment-experienced patients.

George Hanna et al., of Abbott Laboratories, presented pharmacokinetic

data for the new formulation of lopinavir/ritonavir. The new version is a tablet produced by melt-extrusion, a novel technology that allows the active components to be distributed more evenly and absorbed more easily. New dosing (LPV 200 mg + RTV 50 mg) decreases the pill count from 6 to 4 per day. Additionally, the tablets do not require refrigeration and do not contain oleic acid, which is a suspected cause of the lipid abnormalities associated with the soft-gelatin capsule formulation. The PK data, derived from studies of healthy adults who had moderate-fat meals, demonstrated bioequivalence of the two formulations.

An interesting phenomenon in boosted PI therapy is that failure of the regimen does not affect PI sensitivity. Results from the Staccato trial (Ananworanich et al.) showed that 10 patients who failed saquinavir/r + d4T/ddI (or TDF/3TC) did not exhibit the primary PI resistance mutations, though 3 patients had NRTI mutations. This finding echoes reports of failures in the SOLO study (n = 32) and the M98-863 trial (n = 51), involving fosamprenavir/r and LPV/r, respectively: none of these patients showed primary PI mutations at the time of failure.

Earlier this year it was reported that there were substantial reductions in fosamprenavir and LPV levels when the 2 drugs were co-administered with low-dose ritonavir (Kashuba et al., 2005). In contrast, at IAS Duvivier et al. presented clinical and PK data from a study of 20

treatment-experienced patients given the dual-boosted PI regimen of ATV (300 or 400 mg QD) + LPV/r (400/100 mg BID) that showed no apparent adverse PK effect. ATV and LPV serum trough levels were in the target range for 80% and 89% of samples, respectively. Further, the patients fared well clinically, with 69% achieving viral loads <400 copies/mL after 24 weeks – though, notably, 25% experienced grade 2-3 hyperbilirubinemia. Further formal drug interaction studies and clinical trials are certainly warranted.

A continuing challenge in HIV clinical care, said Dr. Hare, is how to deal with the discordant response to antiretroviral therapy – the situation in which the patient achieves viral suppression but does not experience immunologic recovery. Haas et al. reported results of a host genomics analysis conducted in samples from the AACTG repository. Examining single nucleotide polymorphisms (SNPs) in the genes involved in T-cell expansion, survival and apoptosis, the team found that the interferon alpha, interleukin-2 and interleukin-15 genes had haplotypes associated with more favorable CD4+ cell increases on HAART. They also determined, in multivariate analysis, several factors associated with CD4+ cell count increases <200 cells/mm³: older age, male sex, lower pre-treatment viral load, lower pre-therapy CD4+ cell count and hepatitis B antigen positivity. Data from AACTG 5174, a second study looking at discordant response, showed that there is immunologic benefit to be derived from recombinant human growth hormone (rGH) (Smith et al.). The study assigned 60 participants to one of two arms: (A) HAART + rGH (1.5 mg SC QD) for 48 weeks or (B) HAART alone for 24 weeks, then HAART + rGH (3.0 mg SC QD) through week 48. All subjects had at

baseline at least one year of HAART experience, CD4+ cell counts <350 cells/mm³ and viral loads <400 copies/mL. There was a trend toward increased total and naive CD4+ cells in Arm A at week 24, while Arm B experienced no significant change. By week 48, however, there were statistically significant median changes for both groups in total and naive counts: +36 and +26, respectively, for Arm A, and +55 and +23 for Arm B. Similar findings from a local small pilot study with longer duration of rGH treatment (Napolitano et al.) were also reported at IAS. These are promising results, said Dr. Hare, but follow-up off therapy has not been completed and thus long-term clinical significance has not yet been established; he noted as well that the incidence of grade 3-4 clinical events and grade 3-4 lab values is quite high in rGH therapy.

The “New York Case,” involving a highly multi-drug resistant, dual-tropic and rapidly progressing strain of HIV-1 transmitted to a male in NYC, again received coverage at IAS. Blick et al. reported on their effort to identify “Patient Zero,” the source of this MDR strain. To do this, they analyzed approximately 160,000 genotypes made available by Labcorp, Virologic and Quest to compare resistance pathways with that shown by the NYC case. They discovered 2 strains, independently, with matching resistance mutation patterns. These genotypes came from 2 patients in Connecticut, long-term partners who had had receptive anal intercourse with the NYC case in October 2004. In phylogenetic analyses, the viruses were 98-99.5% related. There was no evidence of rapid disease progression, however, in either of the possible

transmission sources, and their viruses were discordant with that of the NYC case in both replication capacity (41% vs. 136%) and viral tropism (R5 vs. dual-tropic). Additionally, the source patients have well controlled viremia and stable CD4+ counts. These facts suggest that the NYC case does *not* represent the highly virulent “super strain” of HIV-1 that the public health community warned about last year, and that host factors are the likely explanation of his rapid progression.

The NYC case challenged the traditional dogma that drug resistant virus slows disease progression because of impaired viral fitness. To assess the relationship of resistance and disease progression, Wensing et al. conducted an analysis of 1,415 patients in the SPREAD cohort who were newly diagnosed in 2003. Twenty percent had become infected within one year prior to testing. There were 78 patients with initial drug resistant virus by genotype; they were matched with 77 randomly selected patients with drug susceptible virus. Endpoints for the comparison were a CD4+ cell decrease >200 cells/mm³, AIDS and initiation of antiretroviral therapy. After a median follow-up of 16 months, 31% of patients with resistant virus had reached an endpoint, compared with 26% of those with pan-sensitive virus. The authors thus concluded that drug resistance is not associated with greater virulence.

Data were presented from the SCOPE study at SFGH regarding

risk factors for transmission of resistance (Chin-Hong et al.). Of 189 patients (77% MSM, 9% MSW, 14% women) in the study with detectable viremia and confirmed genotypic drug resistance, 29% reported unprotected anal or vaginal sex in the previous 4 months with a partner who was HIV negative or of unknown HIV status. The most significant predictor of high-risk sex was found to be methamphetamine use; Viagra use and younger age were also highly predictive, depression and homelessness marginally so.

Finally, Cal Cohen presented the 48-week results of the FOTO ("Five On -- Two Off") trial. The study enrolled patients on stable HAART with undetectable viral load for at least 3 months and CD4+ cell counts >200 cells/mm³. They were switched from a daily treatment regimen to a schedule of 5 days (weekdays) on treatment followed by 2 days (weekends) off. The selected patients were on regimens with efavirenz (n = 10), nevirapine (n = 10) or protease inhibitors (n = 10). All 8 of the patients in the efavirenz cohort who remained in the study had viral loads <50 copies/mL at week 48; this was true for 8 of 9 taking nevirapine and 7 of 9 taking PIs. There were no significant differences in CD4+ counts and no resistance was observed. Adherence was quite good and patients strongly preferred this regimen to standard therapy. Last but not least: there was a 28% reduction in cost. Intermittent therapy is not yet by any means a recommended strategy, but these data certainly suggest that structured treatment interruptions may prove to be a feasible means of simplifying antiretroviral therapy.

Metabolic Complications and Other Adverse Events

Dr. Owen began the second portion of his comments by summarizing a few IAS presentations that dealt with the metabolic changes associated with HIV disease and antiretroviral therapy. First, Dutronc et al. provided information from the Aquitaine cohort, a large French database, regarding incidence of osteopenia, an effect generally thought to be related to HAART. In their analysis of bone mineral density data from 400 consecutive HIV-positive patients, 73% of them male with a median age of 43 years, they found that 54.5% met the criteria for osteopenia (t-score -1 to -2.5) and 25.1% had actual osteoporosis (t-score less than -2.5). Risk factors associated with osteopenia were male gender, AIDS diagnosis and lipodystrophy. We have not seen significant clinical implications of this high prevalence but, if antiretroviral therapy is truly a primary culprit, problems may yet arise as the duration of treatment increases.

Palella et al. presented data gleaned from the MACS cohort regarding the prevalence of the metabolic syndrome, a constellation of symptoms that are often linked to the development of cardiovascular disease. This analysis compared 646 HIV-positive men with 397 who were HIV-negative and confirmed that the likelihood of metabolic syndrome is greater in the context of HIV disease. Specifically, low HDL cholesterol levels and high triglyceride and glucose levels were more likely in the HIV-positive cohort; increased waist circumference, significantly, was more likely among HIV-negative men. Longer time on PIs

was especially associated with greater risk of the metabolic syndrome.

From the international D:A:D study came an evaluation (Sabin et al.) of the influence PIs exert on the development of diabetes risk factors. Antiretroviral therapy has long been thought to affect glucose metabolism; this analysis found that PI use, though not HAART in general, is associated with diabetic risk. The risk in fact increases 5-6% for each year of PI use. However, elevated triglyceride levels, also a risk factor for diabetes in this cohort, also play a part: the PI-diabetes association was no longer significant after adjusting for triglycerides.

The Swiss HIV Cohort Study yielded information, reported by Young et al., regarding the effects of first-line HAART regimens on lipid levels. Following 1065 patients taking either PI-based or NNRTI-based regimens for a median follow-up of 18 months, the study team found that total cholesterol increases were similar for both drug classes. The PIs taken were primarily lopinavir/r, indinavir/r or nelfinavir, and the largest increase (+25 mg/dL/yr) was seen with IDV/r. PI use was also associated with increased triglycerides (+19 mg/dL/yr), especially with ritonavir; there was no such association with NNRTIs. Patients taking NNRTIs had higher increases in HDL-cholesterol than those taking PIs (+4.0 vs. +0.4 mg/dL/yr).

Madruca et al. reported 48-week follow-up results from the ongoing

GS 903e study, an extension of the 903 trial comparing TDF and d4T. GS 903e evaluates subjects who were originally assigned to the d4T arm and, after 144 weeks, switched to the once-daily regimen of TDF + 3TC + EFV. These patients have fared well virologically (92% with HIV RNA <50 copies/mL, by ITT analysis) and immunologically (mean CD4+ cell increase of 37/mm³); but additionally they have had significant improvements in fasting lipids and limb fat. At week 48, the mean change in triglycerides was -72 mg/dL, in total cholesterol -38 mg/dL, and in LDL cholesterol -16 mg/dL. Mean spinal bone mineral density did not change, but limb fat increased by 0.42 kg. TDF thus seems to confer a benefit within the context of these common metabolic complications.

Benn et al. provided further information from the RAVE study regarding the benefits of switching from a thymidine NRTI to either abacavir or tenofovir. Data were reported at the 2005 CROI meeting that showed improvements in peripheral fat following substitution of AZT or d4T with ABC or TDF in 105 adults on HAART with moderate to severe lipoatrophy. At week 48 limb fat increased significantly in both groups, with no difference between drug arms (+316g for ABC vs. +393g for TDF). The data presented at IAS were derived from the evaluation of a subset of 47 patients (23 randomized to TDF, 24 to abacavir) who underwent facial laser scanning technology for the assessment of their facial volume. Cheek volume was shown to increase substantially, with, again, no difference observed between tenofovir and abacavir. This increase was comparable to that seen in individuals receiving a standard collagen treatment to a lipoatrophic area.

Switching PIs is another option for improving lipid profiles, as shown by a German study (Moebius et al.) of 33 subjects who switched from an NNRTI or a PI to atazanavir. Twenty-four weeks after changing, a mean decrease in triglycerides of 46% had occurred. Total cholesterol levels decreased by 18% and non-HDL cholesterol levels were 22% lower. Viral load and CD4+ cell count, meanwhile, did not change significantly from baseline values (mean RNA 72 copies/mL, CD4+ count 455 cells/mm³). The authors suggested that this might be an option for those patients reluctant to start lipid-lowering therapy.

In fact, Calza et al. explored the concept of using a PI-sparing regimen – switching from a PI to an NNRTI – versus starting a lipid-lowering agent. Their study randomized 142 patients (130 evaluable) with mixed hyperlipidemia, all on their first HAART regimen, to 4 arms: (A) switching from a PI to nevirapine (n = 29), (B) switching from a PI to efavirenz (n = 34), (C) starting pravastatin therapy and continuing PI-based HAART (n = 36), or (D) starting bezafibrate and continuing the PI-based regimen. At the end of the 12-month follow-up period, the following mean reductions in triglycerides (versus baseline) were reported: 25.2%, 9.4%, 41.2% and 46.6% for groups A, B, C and D, respectively. The differences between groups A and B and between groups C and D were statistically significant. Results were similar for total and LDL cholesterol levels. Virologic and immunologic efficacy and tolerability were comparable across arms. The authors concluded that switching to a PI-sparing HAART regimen is less effective than using

antihyperlipidemic agents as a means of lowering lipids.

Atazanavir has become a popular PI choice because of its convenient dosing and relatively mild toxicity profile; however, as we know, the drug is associated with significant hyperbilirubinemia. Using the HIV Outpatient Study (HOPS) database, Ward et al. analyzed bilirubin elevations in 218 patients taking atazanavir (147 of them taking RTV as well). The incidence of grade 3 and 4 elevations on the first follow-up measurement was 12.9% in those taking ATV/r and 8.5% among those on unboosted ATV, both quite a bit lower than the levels seen in clinical trials, which were as high as 53%. Higher baseline bilirubin levels and the use of ATV/r increased the incidence and degree of elevation, but neither of these factors is predictive for individual patients. Interestingly, patients with chronic hepatitis did not have a significantly higher incidence of hyperbilirubinemia.

Dr. Owen closed by mentioning a presentation on T-20 and the use of the Biojector 2000 (B2000) needle-free injection system, powered by CO₂, that disperses the drug under the skin (Montaner et al.). This device provides an alternative to the use of standard needles and syringes, which frequently cause injection-site reactions following T-20 dosing. In a study of 32 patients who switched to the B2000 device after receiving regular T-20 injections, a composite score reflecting the severity and number of injection-site reactions was significantly decreased. The

patients reported that the needle-free injector was similar to, or easier than, using needles. Purported advantages of the system include improved dispersion of the medication, consistent injection to an appropriate depth, greater flexibility in choosing an injection site, and fewer issues with biohazardous materials. Some drawbacks, Dr. Owen pointed out, are that (1) the high-pressure CO₂ cartridges cannot go through airport security and (2) the device is currently very difficult to access. Further studies are planned, and the FDA is considering the inclusion of the B2000 data in the T-20 package insert.

Progress in Antiretroviral Roll-Out

The second portion of Dr. Havlir's remarks dealt with issues related to the global epidemic. She began by displaying a world map on which large dark areas, representing areas where 10% or less of people who need antiretroviral therapy are actually receiving it, covered most of Africa and a large part of Asia. As of June 2005, in Sub-Saharan Africa, therapy was available for 11% of those in need of it; in East, South and South-East Asia, the figure was 14%. Worldwide, of 6.5 million people in need, therapy had reached 970,000 of them – 15%. But although it is unlikely that the goal of the WHO “3 x 5” initiative (3 million people treated by the end of this year) will be reached, great progress has been made. Approximately 1 million people in developing countries had received combination therapy as of June – more than doubling from 400,000 in December 2003. Individual targets have been met in Botswana, Thailand, Brazil and, most recently, Uganda. Fourteen low- and middle-income countries have been able to provide coverage for at least half of the people in need. The goal continues to be universal access by 2010.

MTCT

Dr. Havlir next discussed mother-to-child transmission, which continues to be a crucial issue in the developing world. The therapeutic strategy of single-dose nevirapine in MTCT prevention remains an issue because of the risk of developing NVP-resistant virus. James McIntyre's group from South Africa presented data at IAS from the Treatment Options Preservation Study (TOPS), which randomized antepartal HIV-positive women and their newborn infants, who were not breastfed, to receive single-dose nevirapine at delivery or to receive single-dose nevirapine at delivery plus fixed-dose zidovudine/lamivudine for either 4 or 7 days postpartum. They found that coadministration of 4-7 days of AZT + 3TC with single-dose NVP significantly reduced the incidence of NVP resistance. Of 67 mothers receiving AZT/3TC for 4 days, 12% developed NVP resistance; the figure was 10% in the 68 who took AZT/3TC for 7 days. Of the remaining 68, who took just NVP, 60% developed resistance. The Combivir “tail” thus provides a substantial benefit in the MTCT-prevention setting.

Prevention: the Circumcision Study

Dr. Havlir concluded by spending a few minutes discussing the long-standing question of whether male circumcision could be used to prevent female-to-male transmission of HIV infection. Over 30 observational studies have been conducted on this topic; a systematic review and meta-analysis by Helen Weiss led her to conclude that this intervention could reduce the risk of infection by 42%. Randomized controlled intervention trial evidence,

however, was lacking. The Orange Farm Trial (ANRS 1265) was an “acceptability study” designed to assess the effect of circumcision on HIV incidence among young males, and results were presented at IAS (Auvert et al.). The study enrolled over 3000 uncircumcised 18-24 year-old men from Orange Farm (an urban area near Johannesburg) who were willing to be circumcised. They were randomized to immediate circumcision (n = 1550) versus circumcision after 21 months (n = 1538). Following a planned interim analysis, however, the study was interrupted, the Data and Safety Monitoring Board having recognized that the immediate treatment group had fared much better than the delayed-treatment group: 18 HIV cases diagnosed versus 51, respectively. That represented a 65% risk reduction in the treatment group – or 6 to 7 out of 10 potential HIV infections prevented. This is the first randomized controlled trial demonstrating a strong protective effect of safe male circumcision on HIV acquisition by males. The authors acknowledged a few limitations of the study: (1) it represents efficacy in preventing female-to-male transmission, and it may not translate to prevention of male-to-male or male-to-female transmission; (2) the local area in which the study was conducted has a 32% prevalence of HIV infection, and almost all transmission is through heterosexual contact; (3) the study was short-term, so the duration of protective effect is unknown; and (4) protection, though high, was only partial, and safer sex remains

the key element of HIV prevention. It remains to be seen, said Dr. Havlir, whether this will be an effective public health intervention, as there are still questions about where, how, and to what extent male circumcision can be implemented. A few ongoing trials continue to address the issues surrounding this intervention.

Hepatitis Co-Infections

Dr. Hare’s final remarks were dedicated to the conference’s information on hepatitis co-infection issues. There were not a lot of provocative new data, he said, but he had chosen a few presentations of interest. First was an analysis of HCV/HIV co-infected patients in the HOMER cohort in British Columbia (Braitstein et al.) that found an increase in the rate of HCV RNA detection following initiation of HAART. Of 1186 baseline samples tested for the HCV antibody, 51% tested HCV-Ab(+). Among those who were Ab (+), 605 samples were tested for HCV RNA at baseline; 425 (70%) were positive, while 179 (30%) were negative. Out of these 179 patients, 118 had a sample taken 6-12 months following initiation of HAART; of these, 94 (80%) remained negative, while 24 (20%) had detectable HCV RNA. This phenomenon may represent “blips” or laboratory variability (or error), but it may be a function of immune restoration. A late-breaker presentation by Zanini et al. reported on 128 patients co-infected with HIV and HCV (genotype 2 or 3 infection only) who were randomized to receive either 24 or 48 weeks of pegylated interferon alfa-2a combined with ribavirin. The patients were either antiretroviral-naïve with a CD4+ cell count >300 cells/mm³ or on HAART with a CD4+ cell count >200 cells/mm³ and HIV RNA <10,000 copies/mL; all were naïve to

interferon. At 24 weeks, 74 (58%) had negative HCV viremia and could be randomized to stop or continue treatment. Sixty-one percent of the 38 who stopped were HCV RNA negative after 6 months, meeting the criterion for a protocol-defined sustained virologic response (SVR). The same SVR rate (61%) was seen in the 36 who continued therapy; however, only 20 of these patients actually completed therapy to 48 weeks, and among them 90% had an SVR. These results have unclear implications: it seems that a longer course of peg-INF therapy is more effective but, if only half of the patients treated can complete such a course, it may be impossible to deliver therapy. If larger trials confirm the benefit of longer treatment courses, new means of enhancing their tolerability will need to be strategized.

ACTG 5071 suggested that HCV treatment might improve liver histology regardless of virologic response. Lissen et al. reported similar findings from the APRICOT study, which compared pegylated interferon + ribavirin, pegylated interferon alone, and standard interferon + ribavirin. Included in this analysis were 64 patients with cirrhosis or bridging fibrosis who had received at least 2 doses of study drug and had undergone liver biopsies prior to baseline and ≥56 days following treatment. Histologic response was documented in 57% of patients treated with pegylated interferon + ribavirin, 39% of those treated with pegylated interferon alone, and 41% of those treated with standard interferon + ribavirin. Histologic improvement was evident in a third of the patients who did not have an SVR on therapy. A prospective study of treatment

2006 membership renewal

for HCV/HIV co-infected non-responders (SLAM-C) is ongoing.

HCV viral kinetics in co-infected patients differs among particular groups, as Neumann et al. reported. In their small study of patients taking peg-IFN + ribavirin, they found that viral decline was larger and faster in Caucasians (n = 11) than in African Americans (n = 12). This steeper decline is also seen in HCV genotype 2 versus genotype 1. This study found as well that an SVR in co-infected patients on this regimen could be predicted with accuracy at 4 weeks, and possibly as early as 3 days, after treatment initiation – much sooner than the 12 weeks previously reported.

Response to treatment during acute HCV infection is much diminished in patients co-infected with HIV compared to those who are HIV-negative.

Nelson et al. reported results from a study of 50 homosexual, HIV co-infected men with HCV-Ab seroconversion. Twelve of the 50 (24%) spontaneously cleared HCV RNA within 12 weeks, a response associated with low levels of virus and higher baseline CD4+ count. Eleven did not clear, but declined therapy; the remaining 27 were treated for 24 weeks with peg-IFN + ribavirin. Of these 27 patients, 16 (59%) achieved an SVR, a far lower rate than among HIV-negative patients but equivalent to that seen in co-infected patients with chronic HCV. SVR was associated with a higher CD4+ cell count and a higher peak ALT.

Finally, Brau et al. reported results of a retrospective chart review, 1992-2004, in 14 US and Canadian medical centers, comparing progression to hepatocellular carcinoma (HCC) in HCV/HIV co-infected patients (n = 40) versus HCV mono-infected control patients (n = 50). The HCV/HIV patients were found to have been younger at the time of HCC diagnosis (mean age 52 years vs. 61 years) and to have had fewer years' duration of HCV infection (26.4 vs. 35.2). They were far less likely to have used alcohol excessively; AFP levels and other laboratory parameters were significantly higher, as was the proportion treated for HCC. Co-infected patients, in short, develop HCC at a faster rate than those infected with HCV alone.

These remarks concluded the *Report Back from the 3rd IAS Conference on HIV Pathogenesis and Treatment*. Steve O'Brien ended the night by reminding the audience of two upcoming issues facing the medical community: the Medicare Part D benefit change, to take effect January 1, 2006, and the Ryan White reauthorization, in which San Francisco could lose over \$7 million (25%) of its current funding. Regarding the latter, he urged those present to contact their representatives.

The Community Consortium thanks Dr. O'Brien and the panel of speakers, as well as the following organizations that made this evening possible: Auxilium, Boehringer-Ingelheim, Gilead, GlaxoSmithKline, Merck, Roche, Solvay, Tibotec, and Virco.

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 the fact that there are many competing demands and requests for our ever shrinking resources, but we hope you will continue to be able to renew your Consortium membership to allow us to 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 have served as an ongoing model for community based clinical trials and provider education in the country. We do need and appreciate your support! 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!

community consortium turns 20!

The Community Consortium presented “Community-Based Clinical Trials: Triumphs and Challenges” in celebrating 20 years of service to the Bay Area at a gala reception on Wednesday, September 28, 2005. The event was attended by current Consortium members, staff, Community Advisory Board and Executive Advisory Board members, past staff members as well as invited guests.

Dr. Abrams presented a history of clinical-based trials that illustrated the important work the Consortium has produced while becoming a role model for HIV/AIDS organizations worldwide. Donald and the Consortium were presented with certificates of commendation from the San Francisco Board of Supervisors and Mayor Gavin Newsom. Former SF Supervisor and current State Assemblyman Mark Leno presented a special commendation from the State of California.



Assemblyman Mark Leno presents a certificate to Dr. Abrams from the State of California.

The Community Consortium thanks the following organizations that made this evening possible: Abbott, Boehringer-Ingelheim, Gilead, GlaxoSmithKline, Roche, Savient, Tibotec, and Virco.

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, January 23, 2006 at 12PM. If you have any patients you think might be interested, please have them contact Steve Murray, 415-476-9554 x305 or smurray@php.ucsf.edu

executive advisory board

At the Executive Board meeting on August 2, 2005, the members discussed the issue of the Consortium’s role in advocacy for HIV-related issues. As part of its mission, the Community Consortium has a long tradition of advocacy over the last twenty years. There was a Committee on Advocacy and Public Policy that helped focus on these activities. More recently, the Consortium has been addressing these issues on a more *ad hoc* basis.

There are a large number of issues that affect HIV-providers and our patients. A partial list includes: 1. pharmaceutical pricing; 2. access to HIV care; 3. HIV care in penal institutions; 4. federal financing of HIV care, through the Ryan-White program; 5. changes in federal focus on HIV prevention efforts; 6.

methamphetamine use and funding for drug-treatment programs; 7. medical input into the regulation of medical marijuana dispensaries; and 8. patient autonomy in end of life issues (e.g. right to die).

As an organization of Bay Area HIV-providers, who provide services across the entire spectrum of health care institutions, we have a unique opportunity and responsibility to provide expert opinion as issues arise in these areas and others.

If you have interest in this area, or have concerns, we would like to hear from you. You can write or e-mail. In particular, if you would like to become a regular member of a re-formed Committee on Advocacy and Public Policy, please let us know. You can write to the Community Consortium, or e-mail smurray@php.ucsf.edu

project inform IRB

When you conduct clinical research, whether it involves a protocol of your own design or one in which an outside sponsor has asked you to participate (such as an expanded access trial), you must provide assurance of your ability to protect the rights and welfare of your human subjects. Approval by an accredited Institutional Review Board (IRB) provides such an assurance to the trial sponsor, the FDA and any other body associated with the project you plan to undertake.

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.

Clinical Trials Update

SMART (CPCRA 065)

Strategies for Management of AntiRetroviral Therapy is a trial for subjects with CD4+ cell counts greater than 350/mm³ currently on or naïve to antiretroviral therapy. There are two strategies to which patients are randomized in the study. In the Viral Suppression (VS) arm the goal is to use antiretroviral therapy to maintain viral load as low as possible throughout the anticipated six to nine years of study follow-up. In the Drug Conservation (DC) arm, antiretroviral therapy is stopped (or deferred) until the CD4+ cell count drops to less than 250/mm³, at which time episodic antiretroviral therapy is initiated to increase the CD4+ cell count to greater than 350/mm³. Three thousand participants are required per arm for a total target sample size of 6000. Thus far the Community Consortium has enrolled 107 of the 4,868 study participants.

The Community Consortium is participating in two substudies that will take advantage of the initial strategic randomization to compare the rates of development of 1) **anal dysplasia** and 2) **neurologic** complications in the VS and DC arms. The Anal Dysplasia and Neurological substudies have been fully approved, and new SMART enrollees can take advantage of them.

The SMART DSMB Summary dated November 2005 is available online at: <http://www.smart-trial.org/members/dsmb.htm>

If you or your patients might be interested in participating in the SMART study,

please contact Pierre Crouch, R.N., at (415) 476-9554, ext. 333, for further information, or visit the SMART Study website at: <http://www.smart-trial.org/>

GENOMICS

We have currently enrolled 87 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 Community Programs for Clinical Research on AIDS (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. This makes ESPRIT the largest randomized HIV treatment intervention trial to date! 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 study is designed to assess the clinical benefit of IL-2 and hence will follow the 4150 patients worldwide for disease

progression events for a minimum of five years. Participants randomized to the IL-2 arm will repeat cycles of therapy to maintain their CD4+ cell counts at twice baseline or above 1000 cells/mm³. Now that the study is fully enrolled our focus shifts to maintaining participants in follow-up as well as making sure that those individuals randomized to the IL-2 intervention receive cycles of therapy to maintain their CD4+ cell counts at the target level.

Information about your patients enrolled in ESPRIT and whether or not they are at their goal can be found on the ESPRIT website <http://www.espritstudy.org/>

FIRST (CPCRA 058)

The CPCRA's Flexible Initial Retroviral Suppressive Therapies (FIRST) trial, the entry point into the CPCRA's menu of strategic antiretroviral studies for naïve patients, closed on September 16, 2005. The study surpassed its target enrollment and will complete final patient visits before that date. The protocol team has scheduled an unblinding meeting on December 1, 2005. Closeout visits were conducted between September 17, 2005 and November 18, 2005. Stayed tuned for study results.

LTM (CPCRA 060)

The Long Term Monitoring Protocol Team temporarily halted enrollment of the Antiretroviral-Naive Cohort effective June 1, 2004. The planned patient sample size of 1,000 was exceeded.

To date, 3,739 patients are being followed on LTM nationwide, including 173 from our site. We are grateful to the providers who made referrals to this study.

Marijuana for HIV Neuropathy (RCT)

The pilot study of smoked marijuana for patients with painful peripheral neuropathy was completed. Analysis of the 16 patients enrolled revealed that a significant number had relief of their pain resulting in the design of the follow-on randomized placebo-controlled trial. The sample size for the randomized trial was calculated at 50 participants. In the randomized, controlled trial of smoked cannabis, cannabis effectively relieved chronic neuropathic pain from HIV-related painful distal symmetric polyneuropathy (DSP) as well as experimentally induced hyperalgesia. Fifty-six subjects were randomized and 50 completed the trial (25 in each group). Fifty-two percent of patients in the active treatment group reported a greater than 30% reduction in average daily pain, compared to 24% in the placebo group (p=0.04). Smoked cannabis reduced daily pain by 34.9% compared to 13.3% in the placebo group (p=0.04). The magnitude of pain reduction from smoked cannabis is comparable to that reported in trials of the anticonvulsant gabapentin for painful HIV-related DSP.

This study was supported by funding from the University of California San Diego Center for Medicinal Cannabis Research (<http://www.cmcr.ucsd.edu/>).

Observational Cohort Study

The Community Consortium has an ongoing observational cohort study that involves 926 patients being followed predominantly at 8 local sites. As follow-

up matures, this OCS is becoming a valuable resource of information. Here's a breakdown of OCS enrollments by Community Consortium site:

<u>Site</u>	<u>Provider</u>	<u>Enrollments</u>
010	EBAC	388
021	MNHC	243
005	CMHC	189
038	VAMC	60
009	Milton Estes	42
007	CPMC - CA	8
008	Ken Mills	3
012	Robert Scott	2
<u>Total Enrollments</u>		926

Stay tuned for future analyses from this incredible local registry!

Oyster Mushrooms

The Community Consortium is currently enrolling a study of oyster mushrooms. This is a single-arm, 8-week, 20 patient pilot study, evaluating the short-term safety and potential efficacy of oyster mushrooms for treatment of antiretroviral-induced hyperlipidemia in HIV-infected patients. To date, 10 subjects have completed the study. The mushrooms are administered as a freeze-dried powder in individual 15-gram packets, which are added to soups or other foods and taken once a day. 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; patients must not be diagnosed with diabetes

mellitus, and they must meet other criteria for safe study participation. Once enrolled, patients are followed at the General Clinical Research Center (GCRC) at San Francisco General Hospital. They have two overnight inpatient visits and three outpatient visits there over the course of the study. Visits involve completing questionnaires and having blood drawn; inpatient visits additionally include 12-hour pharmacokinetic sampling. 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.

Vaporizer

The Community Consortium has completed its study of 18 healthy individuals, to evaluate the use of a vaporization system as a “smokeless” delivery system for inhaled marijuana and compare plasma levels of delta-9-tetrahydrocannabinol (THC) to those obtained from smoking an identical amount of marijuana from a cigarette using the standardized Foltin puff procedure over a range of THC doses. The study will also attempt to determine if there is a difference in the subjective and objective evidence of cannabis effects between the two delivery systems. The study comparing smoked cannabis with vaporized cannabis was completed in May 2005 and preliminary results suggest that vaporization of cannabis is a safe mode of delivery in which participants had a clear preference for vaporization over smoking.

Twenty-one participants were enrolled to obtain the 18 who completed the 6-day inpatient study. Fifteen men and 3 women, mean age 30 years, were included in the final analysis. The analysis suggests that the peak plasma concentration levels of vaporized cannabis are similar to those of smoked cannabis. Plasma concentrations at 30 minutes after drug administration and beyond were significantly higher in vaporized cannabis as compared to smoked cannabis, however, carbon monoxide levels were significantly reduced with vaporization compared with smoked cannabis.

This study was supported by funding from the University of California San Diego Center for Medicinal Cannabis Research (<http://www.cmcr.ucsd.edu/>).

Other Studies

Screening for Long Term Nonprogressors

In order to understand how the immune system controls HIV replication, the NIAID, NIH Laboratories of Dr. H. Clifford Lane, are currently seeking patients who maintain very low plasma viral loads without antiretroviral therapy to participate in research focusing on long-term non-progression (LTNP) of HIV Infection. The research project entitled "Leukapheresis procedures to obtain plasma or lymphocytes for research studies of HIV-infected patients, including long-term nonprogressor", is being conducted under Mark Connors, M.D., at the National Institute of Allergy and Infectious Disease (NIAID). Inclusion criteria include: adult (at least 18 years of age) HIV-1-infected patient, stable plasma viral loads <5000 copies/mL for a minimum of 3 years, CD4 counts >350 cells/mL for a minimum of 3

years, return visits to NIH at approximately 6-month intervals and willingness to provide informed consent for HLA testing and the storage of blood or tissue samples. Exclusions are pregnant women and antiretroviral therapy (within the previous 3 years). If you have patients who may qualify for this study and are interested in being screened, please contact the Study Coordinator, Mary McLaughlin, at 1-800-772-5464, extension 58001.

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

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), 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://spitfire.emmes.com/study/htr/>.

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. There is some precedence for PrEP, including evidence that antiretrovirals can reduce the incidence of mother-to-child

transmission as well as indirect evidence, from case-control data in health care workers, that post-exposure prophylaxis can be effective. Additionally, a phase I/II safety study of nevirapine as PrEP showed that it was safely tolerated (Jackson et al., *AIDS* 2003). However, another study noted dermatologic and hepatic side effects in HIV uninfected subjects (Patel et al., *JAIDS* 2004), and this, coupled with concerns about NNRTI resistance, has made nevirapine less attractive as a pre-exposure prophylaxis agent.

Tenofovir, meanwhile, has emerged as 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 safety and efficacy trials of tenofovir PrEP either planned or underway, including a study of high-risk women in Africa sponsored by Family Health International and the NIH, and two CDC-sponsored studies of (1) 1200 young heterosexuals in Botswana and (2) 1600 injection drug users in Thailand. To complement these international trials, the CDC has proposed a US trial in MSM. The HIV Research Section of the San Francisco Department of Public Health (SFDPH) sought input from its own Community Advisory Board as well as various community groups in San Francisco prior to considering local participation. Each emphasized the importance of studying the impact of PrEP

on sexual risk behavior in MSM. This issue of behavioral disinhibition is one of the key concerns in PrEP research, and the study designers felt it was important to include a specific evaluation of behavioral change as a result of taking a pill. Finding increased sexual risk would have serious implications for PrEP as a prevention intervention for MSM. Another issue is antiretroviral toxicity – renal, gastrointestinal and bone density effects. These are certainly well documented among HIV-positive individuals; whether the risk/benefit ratio and adverse effects are different in seronegative subjects is unknown. Finally, the emergence of resistant virus is a concern, and the study will closely monitor for this in subjects who seroconvert while on tenofovir.

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 if 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.

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 μm , 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 (415) 353-9745 or moranp@ocim.ucsf.edu, or call the study information number: (415) 353-9744.



**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/staying_well**