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2005 educational offerings

REPORT BACK FROM THE 12th CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS (CROI)

Wednesday, March 9, 2005
6:00 PM – 8:30 PM
Genentech Hall Auditorium
Mission Bay Campus – UCSF
600 16th Street @ Owens

Speakers:

Harry Lampiris, MD
Stephen Follansbee, MD

See *Future Synopsis*
announcements for other 2005
Educational CME Programs

upcoming conferences

12TH CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS (CROI)

February 22-25, 2005
Boston, Massachusetts
<http://www.retroconference.org/2005/home.htm>

3RD INTERNATIONAL AIDS CONFERENCES AND IAS CONFERENCE ON HIV PATHOGENESIS AND TREATMENT (IAS)

July 24-27, 2005
Rio DeJaneiro, Brazil
<http://www.iasociety.org/>

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

September 21-24, 2005
New Orleans, Louisiana
<http://www.icaac.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.

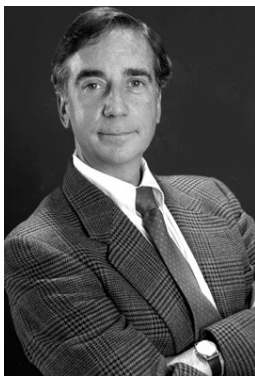
executive advisory board

The schedule of meetings of the Community Consortium Executive Advisory Board is April 27, August 3, and October 26, 2005. Meetings take place at 7:30 AM in the conference room at the Community Consortium.

congrats wally!

The Community Consortium would like to recognize Dr. Walter Krampf, for his many years of service to the Community Consortium as a member and Executive Advisory Board Member. Dr. Krampf will be retiring as of March 2005. The Consortium would like to give heartfelt thanks to Dr. Krampf for his tireless efforts in support of the Consortium, our studies and staff. Dr. Krampf's presence will be truly missed at the Consortium. We wish him nothing but the best in his retirement, as he truly has earned it!

Happy Winter!



Donald I. Abrams, M.D.,
Editor



Paul Couey
Guest writer

The Community Consortium presented a *Report Back from the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy* on November 17, 2004, at UCSF Mission Bay's Genentech Hall auditorium. The event was hosted by Steve O'Brien, MD, Director of the East Bay AIDS Clinic. The featured speakers were Michael Horberg, MD, FACP, Director of HIV/AIDS Policy, Quality Improvement and Research for Kaiser-Permanente, Kathy Mulligan, PhD, Associate Professor of Medicine at UCSF, and Ian McNicholl, PharmD, Clinical Pharmacy Specialist at the UCSF Positive Health Program at San Francisco General Hospital. Dr. O'Brien began the evening by introducing the speakers and briefly outlining the topics to be discussed.

Once-Daily Regimens

Dr. Horberg led off with a discussion of several ICAAC presentations on once-daily regimens. The first of these concerned 24-week data from the VEST study (Cohen et al.), an ongoing trial in which patients with viral load <50 copies/mL who are currently taking a protease inhibitor and 2 nucleosides are switched to a non-PI regimen. Presently 186 patients have been enrolled of a planned 300. Upon enrollment patients are randomized 1:1 to receive either efavirenz + ddI EC + 3TC (all qd) or efavirenz with their current nucleosides. Results at 24 weeks show no difference in viral efficacy (86% of both groups achieving viral loads below the limit of quantification) and no significant difference in adverse events. There has been no pancreatitis among patients taking ddI. At week 24 on efavirenz, 73% of patients had 100% adherence, compared to 57% at baseline that were fully adherent on PIs. It is interesting, Dr. Horberg pointed out, that the remaining 43% of those baseline patients who were not completely adherent had nevertheless achieved control of their viral loads.

Previous studies have shown a higher than expected incidence of virologic failure with the combination of full-strength ddI and tenofovir (TDF), and there have been reports of pancreatitis and impaired renal function. In fact, based on earlier evidence, Bristol Myers Squibb recently sent out an Alert to Clinicians, cautioning against using these agents in combination with non-nucleosides in naive patients. What has not previously been emphasized is the attenuation of CD4 cells. Negredo et al. presented data concerning CD4+ cell count changes after ddI dose reduction (400 mg to 250 mg) in HAART regimens containing ddI and TDF. Thirty-nine patients on the TORO study, having taken ddI 400 mg, TDF and either a PI or NNRTI for at least 12 months, were classified as either "CD4 decline" or "CD4 maintained." The CD4 decline group ($n = 20$) had experienced a mean decline of 86 cells over the 12 months, and the CD4 maintained group ($n = 19$) had had a mean increase of 85 cells. All 39 patients reduced their ddI dosage to 250 mg and were followed for 36 weeks, at which point the CD4 maintained group had held steady and the CD4 decline

group had experienced a significant mean increase in cells (though still lower than baseline). Thus, even with the reduction in dose, the ddI+TDF combination seems questionable.

Tenofovir

Dr. Horberg next mentioned two studies involving TDF qd regimens. The first (DeJesus et al.) looked at once-daily Trizivir and TDF in a HAART-naive cohort of 123 patients. By intent-to-treat (ITT) analysis, 64% had viral loads <50 copies/ml at 24 weeks, compared to 85% by the as-treated analysis. Dr. Horberg praised the authors for accounting for the patients dropped from treatment, stating he would like to see this done more often in study presentations. Twenty-seven patients discontinued prematurely. Twelve of these discontinuations were due to adverse events (8 with abacavir hypersensitivity reaction, 2 with nausea, 1 with “mood swings,” and 1 with cancer); the remainder were due to protocol issues, including loss to follow-up. There was a median gain of 80 CD4 cells/mm³. The second study (Gazzard et al.) compared TDF + emtricitabine (FTC) + efavirenz vs. Combivir + efavirenz. At week 24, 73% of the TDF/FTC group (*n* = 255) had viral loads < 50 copies/mL, compared to 64% in the Combivir group (*n* = 254). Among patients with baseline viral loads > 100,000 copies/mL, 67% in the TDF/FTC group vs. 54% in the Combivir group attained viral loads <50 copies/mL. The incidence of K103N and M184V mutations was equal in both arms, and the K65R mutation was not seen.

T-20

Dr. Horberg next discussed a study (Thompson et al.) that examined the pharmacokinetics and safety of once-daily vs. twice-daily enfuvirtide (T-20). This 14-day trial featured a cross-over design such that patients were randomized to a T-20 regimen of either 180 mg qd or 90 mg bid (with optimized background antiretroviral therapy) for the first 7 days, and then switched to the other regimen for days 8-14. The two groups were well matched in baseline demographics. Interestingly, 41% of the patients had no genotypic sensitivity to any of their background antiretroviral agents. Intensive pharmacokinetic sampling at day 14 showed that mean T-20 plasma concentration was well below the IC₅₀ in both regimens; further, both regimens achieved a >1.5 log₁₀ reduction in HIV RNA. A larger trial is planned.

There were two other notable presentations regarding T-20, from secondary analyses of the TORO study. Katlama et al. found that the week 12 response to therapy is a predictor of the treatment outcome. Of 395 study patients whose viral loads dropped 1 log₁₀ or greater by week 12, 79% sustained that response through week 96; in contrast, only 9% of the remaining 225 patients (with viral load reductions of <1 log₁₀ at week 12) had ≤1 log₁₀ drops at week 96. The CD4 responses were similar, i.e., a CD4 boost of more than 50 cells/mm³ at week 12 was predictive of a sustained response.

The other study, by Wat et al., looked at serum IgE levels on T-20. Dr. Horberg noted that he has had concerns about antigenic (particularly IgE-mediated) response on T-20 over time, given the associated risk of eosinophilia. This study found, however, that by week 24 the percentage of patients with elevated IgE levels dropped substantially from baseline

in both the T-20 and the optimal-background-only arms (nearly 50% to <5% in each arm). There was no correlation between IgE levels and CD4 cell counts. There was, at baseline, a statistically significant correlation between elevated IgE levels and eosinophilia, but this was not sustained through the course of the study.

Lipids

Dr. Horberg finished this first segment of the program with coverage of two presentations on antiretrovirals and lipids. The first of these concerned a follow-up by Nadler et al. of the NEAT trial, an efficacy study of fosamprenavir (FPV) vs. nelfinavir (NFV). At 48 weeks, the FPV group had experienced a 37% increase in HDL cholesterol, compared with a 22% increase in the NFV group – not a statistically significant difference – and no significant change in total cholesterol or triglycerides was seen in either group. The second presentation (Suleiman et al.) dealt with Gilead’s substudy 903E, in which 85 patients exchanged d4T for TDF. At 24 weeks, 81 of 82 patients had viral loads <50 copies/mL, and there were significant decreases in triglycerides as well as total and LDL cholesterol levels. There were also, Dr. Horberg noted, smaller but still statistically significant decreases in HDL levels.

Body Habitus Alterations

Dr. Mulligan provided an update from the International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, which immediately preceded ICAAC and was the forum for the majority of new metabolic data. This annual meeting focuses on the past year’s research developments in lipodystrophy

and metabolic complications, and the impact of these developments on clinical practice. In this first segment of her update, Dr. Mulligan dealt with body habitus changes, with particular attention paid to therapeutics.

She noted that she had attended the Forum for Collaborative HIV Research, at which various representatives from the FDA provided their perspective on clinical endpoints for antiretroviral toxicities and for the efficacy and safety of interventions for body habitus alterations. Regarding safety endpoints for antiretroviral trials, the commonly monitored lab values (lipids and glucose) are considered defining; other lab values, such as insulin and insulin resistance, should correlate with clinical changes, e.g., diabetes. Morphologic changes (facial wasting, fat loss in limbs, central fat accumulation) should be specifically identified; “lipodystrophy” is a good word to describe all of the changes, but the FDA finds it too ambiguous for specific labeling purposes. Regarding interventions for morphologic abnormalities, the FDA is interested in objective measurements of change (by CT, DEXA, anthropometry, ultrasound), but they also want to know if the changes are clinically relevant by such indices as quality of life, photographs and biochemical data. Dr. Mulligan felt that this information helped to lay a framework for evaluating the efficacy of interventions for body habitus changes.

The list of potential interventions for lipoatrophy is fairly short. Most of the research has focused on nucleoside analog (NRTI) substitution; additionally, thiazolidinediones and surgical implants are under investigation, and some very preliminary work has begun with uridine.

NRTI Substitution

A group in western Australia (Nolan et al.) presented some data that are relevant to predicting success from NRTI substitution. Their ongoing study involves taking biopsies of suprailiac subcutaneous fat and analyzing mitochondrial DNA content. In cross-sectional analysis they had previously found that mitochondrial DNA levels were comparable in patients who were HIV-negative ($n = 7$), those who were antiretroviral-naive ($n = 34$), those on a regimen with no NRTI ($n = 7$) and those on thymidine-sparing regimens ($n = 23$). Levels were lower in patients taking AZT ($n = 42$), and lower still in those taking d4T ($n = 35$). The newly presented findings concerned serial mitochondrial measurements in patients who switched. Those who switched from d4T to AZT had prompt increases in mitochondrial DNA (from 3 to 12 months); switching to a non-thymidine regimen brought levels back to the normal range. Based on these results one might predict some reversal of fat atrophy.

In fact, recently published results of the MITOX and TARHEEL studies (Martin and McComsey, respectively) showed that switching abacavir for d4T does provide an improvement in peripheral fat. The changes, however, occur slowly and are detected by DEXA before they are perceptible to the patients. At the Lipodystrophy Meeting, data were presented from an open-label study in Greece (Tsekes et al.) in which patients

were switched from d4T to TDF. Over a year, they gained about 1.2 kg of fat in the arms and legs – a statistically significant change but, again, not a rapid one, considering the prompt reversal of mitochondrial DNA levels.

Uridine

Thus, other interventions are sought, including the use of uridine. Uridine is a pyrimidine, and it is thought that pyrimidine pools in mitochondria may be depleted by inhibition of electron transport function. Increasing this pool from an external source could potentially overcome some of the limitations imposed by thymidine analogs. Ulrich Walker presented data from a study of mouse fat cells, showing that mitochondrial DNA levels are deranged by d4T and ddC and that the coadministration of uridine can prevent that derangement. This was a small study, and it remains to be seen whether uridine can normalize already depressed mitochondrial DNA levels, or whether these results are reproducible in humans (assuming we can achieve the physiologically relevant concentrations). The answers to these questions could have treatment implications for those patients who have had fat atrophy but wish to continue taking thymidine analogs.

Surgical Implants

Dr. Mulligan said that, as a co-chair of the Lipodystrophy Meeting, she has often heard criticism from the HIV community for not including oral presentations on plastic surgery. In previous years there was not felt to be any compelling new information. Happily, however, this year’s program included an interesting presentation of 24-week data from an Italian study (Guaraldi et al.) comparing

surgical interventions for facial lipoatrophy. The study involved a partial randomization to three groups: patients with sufficient subcutaneous (SC) fat were assigned to the autologous fat transfer arm ($n = 24$), and patients with inadequate SC fat were randomized to receive either poly lactic acid injections ($n = 20$) or polyacrylamide injections ($n = 15$). Autologous fat transfer, or lipofilling, involves removing SC fat, usually gluteal, and reinjecting it into the atrophied area. Study results included both objective and subjective findings: improved dermal fitness by ultrasound, and a marked improvement in self-perceived appearance by visual analog scale. Because data is limited to the 24-week follow-up, durability of effects remains uncertain; however, although a few patients (16%) in the autologous fat transfer arm experienced “hamster syndrome” (excessive fat growth after transfer), all three procedures were fairly well tolerated, and efficacy in each was similar.

Human Growth Hormone

Turning to central fat accumulation, Dr. Mulligan noted that there appear to be a few more therapeutic options: diet and exercise, metformin, human growth hormone (HGH), HGH releasing factor, testosterone replacement and, again, thiazolidinediones. Many of the studies to date have focused on HGH, at various doses (6, 4, 3, 2 and 1 mg/day). It has for some time been suggested that HGH releasing factors might be used to achieve a more physiologic means of administering HGH. One presentation (Grinspoon et al.) at the

Lipodystrophy Meeting addressed this, discussing results of a study of TH9507, an HGH releasing factor, in patients with abdominal fat accumulation. Sixty-one patients were selected for the presence of an increased waist circumference and an elevated waist/hip ratio, and randomized to receive TH9507, at 1 mg ($n = 19$) or 2 mg ($n = 21$) per day, or placebo ($n = 21$). There were 48 patients who completed the 12-week study. There was little activity seen at the 1 mg/day dose; at 2 mg/day there was a statistically significant reduction in visceral fat compared to baseline, but it was not significant when compared to placebo (perhaps because of sample size limitations). Other effects of the 2 mg/day dose – a slight increase in HDL cholesterol, decreased total/HDL cholesterol ratio, lower triglycerides and increased fasting insulin levels – were similar to those seen with growth hormone. There were no significant differences in adverse events among the groups; notably, however, 11 of 21 patients in the 2 mg/day group complained of headache and paresthesia - side effects we associate with IGF-1. These are intriguing preliminary results, though it would seem that a larger sample size is needed to make a real determination of effect. A phase III trial is in progress.

Dr. Mulligan concluded this portion of her remarks with a plug for two clinical trials currently underway at SFGH, both open-label proof-of-principle studies. The first study is investigating IGF-1, bound to its major binding protein, IGFBP-3, for central fat accumulation and insulin resistance. The second is a study of Leptin for metabolic complications of lipoatrophy. Those interested in further information about these studies should call Viva Tai, at (415) 206-4090.

Investigational Antiretrovirals/Drug Interactions

Dr. O’Brien next welcomed Ian McNicholl to the podium to discuss data presented at ICAAC regarding investigational antiretroviral agents. Dr. McNicholl opened by pointing out that, although it may not seem clinically relevant to discuss these compounds while they are still in the investigational stage, in fact the trials are going on in San Francisco and they include, or seek to include, some of our patients. So it behooves us to be familiar with the antiretroviral pipeline, which, compared to just a few years ago, is quite prolific. And it is good to know that there are promising therapies on the horizon for the many patients who have exhausted all other options.

Reverset and SPD754

There was new data presented (Murphy et al.) from the D-d4FC (Reverset) trial of 8 experienced patients who completed 10 days of monotherapy. At baseline, all patients had viral loads >1000 copies/mL and CD4 cell counts >50 cells/mm³; five had the M184V mutation and four had ≥ 3 thymidine analog mutations (TAMs). All subjects combined had a 0.8 log₁₀ viral reduction at day 11; however, those with 3-4 TAMs experienced a 0.4 log₁₀ drop. So Reverset’s niche is unclear. How many pre-existing TAMs can a patient have and still expect clinical efficacy on treatment?

Data from Cahn et al. on SPD754, a deoxycytidine analog, showed a good dose response, particularly at the 1200mg and 1600 mg doses, in another 10 day monotherapy trial; however, the focus of the presentation was the drug’s resistance profile. The study found that there was a

significant viral load reduction with up to 5 pre-existing TAMs, with only a 1.8 fold decrease in susceptibility and activity maintained against M184V. Notably, SPD754 appears to be antagonistic toward concomitant 3TC. The dose, either 1200 mg or 1600 mg daily, will probably need to be divided based on drug half-life.

Capravirine

Though there was no information on capravirine (CPV) clinical trials, there was data on CPV drug interactions. CPV is a non-nucleoside analog and, like the other NNRTIs, it has a profound effect on P450 CYP3A4 metabolism. We knew already that Kaletra increases CPV levels fivefold, and that CPV in return decreases Kaletra levels; the proper dose adjustment when these two drugs are combined has not yet been determined. Agouron-Pfizer is pursuing combining CPV with either nelfinavir or Kaletra. The ICAAC presentations concerned combining CPV with other agents, specifically escitalopram and phenytoin. Raber et al. found that when CPV is given with the antidepressant escitalopram, the escitalopram AUC is decreased 18%; however, adding Kaletra to this combination decreases the escitalopram AUC 32-45%. Because escitalopram is a serum serotonin re-uptake inhibitor, and all SSRIs are similarly metabolized, we can extrapolate that a slightly higher dose would be required for any SSRI coadministered with CPV, or with CPV and Kaletra; the exact dose adjustment, again, has not been determined. Amantea et al. showed

that the anticonvulsant Phenytoin, when given with CPV and Kaletra, is reduced 30-33%; increasing the Kaletra dose to 4 capsules BID to compensate for this effect can sharply increase LFTs. In short, this combination is not recommended.

Tipranavir and TMC114

Of the protease inhibitor class, the PI closest to market is tipranavir (TPV). It requires dosing with ritonavir, which must be prescribed separately. Its niche, at the moment, appears to be within a salvage regimen, as it has shown efficacy against pre-existing PI mutations. Hicks et al. reported on a 24-week planned analysis of the RESIST-1 study, comparing TPV/r to several other PIs (lopinavir, indinavir, saquinavir and amprenavir), each boosted by ritonavir, in quite highly experienced patients (median 15 baseline mutations and 12 prior antiretroviral drugs). At 24 weeks, 25.1% of the TPV/r arm had achieved viral loads <50 copies/mL versus 10% of the comparator PI arm. Those patients using T-20 as part of their treatment regimen reached <50 copies/mL at rates of 32.8% and 14.3%, respectively, which were statistically significant differences.

TPV/r patients in the study experienced significantly higher percentages of grade 3 and grade 4 liver enzyme and lipid elevations, the laboratory abnormalities most commonly reported. The most commonly reported adverse events were gastrointestinal in nature and included diarrhea, nausea and vomiting, fatigue, anorexia, dehydration, and headache. The event rate did not differ significantly between arms; however, only grade 3 and grade 4 incidences were reported. Dr. McNicholl said he would be interested in knowing grade 1 and grade 2 rates, since lower grade toxicities could certainly affect whether or not patients tolerate the drug.

As with other PIs, there are possible drug interactions to consider with TPV (Van Heeswijk et al.). The TPV interaction with clarithromycin is minimal, but it does significantly reduce the metabolite in clarithromycin active against community acquired pneumonia and H. influenzae. More pertinently, TPV causes a substantial increase (nearly 200%) in rifabutin levels, both the parent compound and its active metabolite; administering these drugs concomitantly will necessitate a dose reduction in rifabutin to 150 mg q3d. Previous presented interaction data showed TPV decreasing levels of other PIs as well as oral contraceptives, and increasing fluconazole levels.

Little was presented about TMC114, another PI that requires boosting with ritonavir. However, Hoetelmans et al. did have new information on its rather minor interaction with atorvastatin. Notably, when TMC114/r and atorvastatin are dosed together there are no active metabolites of atorvastatin detectable. It appears that a higher atorvastatin dose may be required for clinical efficacy.

CCR5 Antagonists

Turning to a newer drug class, the CCR5 antagonists, Dr. McNicholl first reviewed a presentation (Lewis et al.) on the emergence of dual-tropic (R5/X4) virus during monotherapy with UK-427,857, a CCR5 antagonist compound. Two patients who had received the compound for 9 days were found to have dual-tropic virus. The first patient was found, retroactively, to have exhibited this dual tropism on baseline genotype. At day 11 the genotype was unchanged; thus, there was no viral evolution on the CCR5 antagonist therapy. This patient had a

0.7 log₁₀ reduction in viral load. The second patient, who had a 1.3 log₁₀ viral load reduction, was not noted to have dual-tropic virus at baseline; however, it was detected at day 11. Whether it was pre-existing (and not detected by the baseline assay) or emerged during UK-427,857 therapy could not be determined.

In a second study, Moyle et al. analyzed 863 samples to look at the prevalence of X4- or R5/X4-tropic virus at CD4 counts ranging from 300 to <50 cells/mm³. Results and Failures that as the CD4 count decreased utilization of the R5 receptor also decreased, and there was a corresponding increase in use of the X4 receptor. Additionally, it was shown in yet another study (Demarest et al.) that use of the X4 receptor was more common in antiretroviral treatment-experienced patients. Dr. McNicholl's impressions from the above three abstracts were that (1) we need better assays to be able to determine the presence of X4-tropic virus prior to treatment and (2) we are still unclear what role, if any, CCR5 antagonists will have in the treatment of patients with low CD4 counts.

A final CCR5 antagonist presentation (Lalezari et al.) concerned the 873140 compound. In 10 days of monotherapy, a clear dose response relationship emerged, with doses ranging from 200 mg to 1200 mg daily. In the cohort receiving 600 mg BID (*n* = 8), 100% of the subjects achieved a reduction in viral load that was 1.0 log₁₀ or greater (mean reduction 1.66 log₁₀). Viral tropism was evaluated

throughout treatment and at day 24. One subject in the 200 mg QD cohort showed R5-tropic virus at day 1, dual/mixed-tropic virus at day 10, and R5-tropic virus again at day 24. Preliminary analysis of this subject demonstrated that dual-tropic virus was present at baseline but below the assay's limit of detection – again pointing to the need for a better assay. Adverse events in this short trial were mostly gastrointestinal in nature and generally resolved within 1-3 days of therapy.

Resistance and Failures

Dr. Horberg began his second round by discussing antiretroviral resistance. He began with Virologic's presentation on resistance prevalence in the US (Ross et al.), which utilized a retrospective review of data on 317 HAART-naïve patients in 40 cities in 2003. Of these patients, 23% were resistant to at least one drug, and 8% had an NRTI mutation. Reduced susceptibility to ≥1 NNRTI was detected in 18%; 6% had reduced susceptibility to ≥1 PI. Demographically, 27% were Caucasian, 23% African American, and 24% MSM. The findings underscore the need for resistance testing prior to initiating therapy.

Of particular interest to Dr. Horberg was a UNC study (Edwards et al.) of resistance evolution in 98 patients with virologic failure and no change in HAART between two genotypes obtained ≥30 days apart. The breakdown of regimens was as follows: 55% PI, 14% NNRTI, 14% PI and NNRTI, and 15% NRTI only. According to the first genotype, 86 subjects had ≥1 mutation and the median number of mutations was 3. By the next genotype, 91 subjects had ≥1 mutation and the median number of mutations was 4; of these 91 subjects, 27% had 1 new mutation, 12% had 2, and 21% had 3 or more. Thus,

moderate evolution does occur on a failing regimen. The study found statistically significant risk for new mutation associated with (1) having 0 mutations at baseline, (2) having a CD4 cell count <200 cells/mm³ and (3) having 2-5 years HAART experience. Surprisingly, those with higher viral loads showed little viral evolution. The authors concluded, though, that once virologic failure is noted it is probably *not* a good idea to “wait and watch” before changing the regimen, since viral evolution is ongoing.

In an effort to address questions many people have about race as a predictor of failure, Guest et al. performed a retrospective analysis of 626 patients at the Atlanta VA who had initiated therapy with either efavirenz or lopinavir/r based regimens. African-American vs. Caucasian cases were followed for either immunologic failure (CD4 count rise ≤50 cells/mm³ after ≥3 months on therapy) or virologic failure (viral load >400 after ≥3 months on therapy). Race was not at all associated with virologic failure; however, African-Americans experienced greater sustained CD4 cell increases with efavirenz than Caucasians. Race was not at all predictive in lopinavir/r regimens.

The next study dealt with intermittent low-level viremia, or viral “blips”. Nettles et al. followed 10 patients with generally suppressed viremia but occasional blips, checking viral loads 3 times weekly for 12-16 weeks and obtaining genotypes with any viral load increase. Samples were sent to two separate labs, and the κ value (level of agreement between the two labs) was a quite poor 4.4%. Eighteen blips were found, with a median value of 0.67 blips/month, and the median duration of

blips was 60 hours. There was no correlation with any demographics, CD4 count, type of regimen or clinical condition at the time of the blip, and no genotypic changes were seen with any blip. The investigators concluded that blips of <120 copies/mL may be lab error.

An Abbott study (Pierone et al.) looked at resistance in 33 patients from 2 other studies who had experienced virologic failure (defined as 2 or more viral loads >400 copies/mL or never having reached <400 copies/mL) and then initiated lopinavir/r monotherapy. Data at week 24 from the 18 subjects who had previously been on NNRTI-based regimens showed that 13 had viral loads <75 copies/mL, three had discontinued because of Kaletra-induced diarrhea, and only two had failed therapy.

In a final resistance-related presentation, Rodriguez et al. described the therapeutic intervention of Trizivir + TDF in patients experiencing early virologic failure on an initial antiretroviral regimen of either AZT or d4T with 3TC and a PI or NNRTI. To be eligible, patients had to have viral loads of 400-10,000 copies/mL and CD4 counts >100 copies/mm³. The key exclusion criterion was >2 NRTI mutations or the K65R mutation. At baseline, 61% had been on a PI, 39% on an NNRTI; the median CD4 count was 436/mm³. At the end of 24 weeks, 80% of the subjects had an HIV RNA <50 copies/mL by on-treatment analysis; 65% had <50 copies/mL by intention to treat. There was no

significant change in CD4 count, but this was not surprising given the high level at baseline. These results suggest that a quadruple NRTI regimen can successfully be used to counter early virologic failure, thereby sparing other drug classes and providing a low pill burden.

Potpourri

Syphilis

Dr. Horberg continued with what he termed “miscellaneous notes on a variety of subjects,” beginning by reporting on a syphilis seminar that raised several important points. First, though work is going forward on creating a vaccine, *T. pallidum* is not a single subspecies and a vaccine will be hard to generate. Moreover, the *T. pallidum* spirochetes must be grown in rabbits, which makes it difficult to obtain sufficient numbers for analysis. Second, there is very limited data on any therapy other than penicillin. There is currently a large-scale study in the U.S. and Uganda involving azithromycin, but early failures are being reported. And third, although the CDC defines success in syphilis treatment as a 2-fold reduction in the VDRL or RPR at 6 months, the response is often slower, especially in HIV-positive individuals. Also, as recently reported by Rolfs in *NEJM*, 21% of HIV-positive patients studied did not respond (by VDRL) to penicillin therapy at 12 months, and there are currently no treatment recommendations for such failures.

Hepatitis Co-infection

There were two presentations relating to Hepatitis C co-infection. Rodriguez-Torres and colleagues reported APRICOT study results on the predictability of a sustained virologic response (SVR) with pegylated IFN + ribavirin. Of 289 treated subjects,

only 116 had an SVR (HCV viral load below the quantifiable limit) at the end of the 72-week post-therapy follow-up. Of these 116 subjects, 99 had a >2 log drop in HCV viral load after 4 weeks of therapy; however, 114 of them had achieved such a response by week 12. The conclusion here was that a reliable SVR prediction cannot be made at week 4, and treatment should continue to be carried out to week 12, as currently recommended. Soriano et al. in Madrid, performing retrospective analysis of 351 co-infected patients, provided some characterization of long-term response vs. failure. Only 77 of these patients (22%) achieved SVR, and the response rates were similar among the 3 treatment regimens (IFN only vs. IFN/ribavirin vs. pegylated IFN/ribavirin). There was no difference in demographics or genotypes between responders and non-responders; nor did HIV course (CD4 count, viral load, treatment regimen) differ. In short, no predictors of treatment success were detected. Of note, among the 274 patients who did not achieve SVR, 90% had persistent transaminitis following therapy; however, over the 5-10 year follow-up, only 4% developed cirrhosis and 2 died with end-stage liver disease.

Another Spanish trial (Martin-Carbonero et al.) examined the triple threat of HIV + hepatitis C + hepatitis B. Previous studies in HCV/HBV patients have shown that subjects who were hepatitis B surface antigen positive (HBsAg+) were better able to clear their HCV viral loads than those who were HBsAg-; however, these studies had not been performed in triple-infected subjects. This cross-sectional comparative study obtained the same findings among persons with HIV: 68% of HBsAg+ subjects cleared their HCV vs. 10% of those who were

HBsAg-. The level of HBV viral load made no difference in this effect, nor did treatment with TDF or 3TC; in fact, by multivariate analysis, a positive surface antigen was the only difference found.

Miscellaneous

Dr. Horberg closed by mentioning three studies in brief. Salvato et al. examined biweekly erythropoietin therapy for anemic patients, finding that quality of life measures improved significantly with increased hemoglobin levels – though there was an 8.9% incidence of diarrhea. Capparelli and colleagues studied the stability of lopinavir/r at higher temperatures and found that the capsules can last up to 30 days at 35°C, but break after 24 hours at 45°C. This has implications for treatment in sub-Saharan Africa but is also apparently of interest to the U.S. military. Finally, Aronson et al. at Walter Reed performed cross-sectional analysis of bone mineral density DEXA data from 267 HIV-positive volunteers, finding 6% osteoporosis and 40% osteopenia among them. These rates were not related to HAART, CD4 count or years of disease; the only significant risk for low bone mineral density was, in fact, African –American race.

Insulin Resistance

Dr. Mulligan continued her update from the Lipodystrophy Meeting with coverage of new data on insulin resistance. She stated that, though HIV practitioners hear a great deal about lipid abnormalities, she feels insulin resistance is an underappreciated component of the

metabolic syndrome. She therefore had decided to discuss a series of presentations on the topic, starting with research from outside the HIV realm and continuing with results from HIV metabolic specialists.

Incidence in General Population

The metabolic syndrome has been defined in similar fashion by the World Health Organization (WHO), in 1998, and the National Cholesterol Education Program (NCEP), in 2002. Both definitions include measures of glycemia and obesity, triglyceride elevations, and blood pressure abnormalities; the WHO definition also includes microalbuminuria.

In a plenary presentation, Enzo Bonora provided interesting study results on metabolic syndrome prevalence in the 40-79 year-old population of the town of Bruneck, Italy. In a random sample of over 800 participants, the prevalence was found to be approximately 35% (by WHO definition); associated factors were age and elevated body mass index (BMI), with no significant difference between genders. A 5-year follow-up of participants showed that those with metabolic syndrome were significantly more likely to develop carotid plaques and stenosis, as measured by ultrasound. Much of Dr. Bonora's study focused on insulin resistance's role in cardiovascular disease. Despite adjusting for a variety of other risk factors, e.g., age, sex, hyperlipidemia, hypertension, BMI, insulin resistance remained a significant independent predictor of disease.

In another plenary talk, Rob Hegele listed a number of inherited insulin resistance syndromes, including familial partial lipodystrophy (FPLD). FPLD has been linked with mutations in the LMNA gene that break down nuclear integrity and cause cells to become nonfunctional, leading to adipose tissue loss, metabolic dysregulation

and, ultimately, increased risk of cardiovascular disease. In fact, Dr. Hegele examined Canadian public health records for the national rate of coronary artery bypass graft procedures performed in women and found that, while the overall CABG incidence in women aged 35-54 was 1 in 1129, among LMNA mutation carriers the incidence was 1 in 3.5 – strong evidence of accelerated cardiovascular disease risk.

Incidence in HIV

Dr. Mulligan noted the phenotypic similarities between Bonora's metabolic syndrome and Hegele's FPLD - fat accumulation and fat loss, insulin and lipid derangements, increases in blood pressure and markers of inflammation – and remarked that these elements were seen as well in persons with HIV infection. It is unclear, then, whether the metabolic alterations in HIV disease are overlapping or additive. Multiple factors may account for insulin resistance in HIV: the metabolic syndrome seen in the general population, central fat accumulation, lipodystrophy, and direct effects from antiretroviral therapy.

Grace Lee and Carl Grunfeld, from SFGH, reported on ritonavir and insulin resistance. They gave a single dose of ritonavir (in the therapeutic range) or placebo to HIV-negative subjects during euglycemic-hyperinsulinemic clamp and found that insulin-mediated glucose uptake was significantly lower in the ritonavir group. So what of boosted regimens containing ritonavir? A British study (Doran et al.) looked at atazanavir/r, indinavir/r and placebo, again using the glucose clamp technique, and found that boosted indinavir impaired insulin-mediated glucose uptake while boosted atazanavir did not; indeed, this impairment has been seen in

previous studies when indinavir was given alone. In various studies of acute and long-term effects of PIs on insulin sensitivity in healthy volunteers, the reduction in sensitivity has ranged from 17% to 34%. But, Dr. Mulligan pointed out, a 34% reduction in insulin sensitivity with a PI does not tell the whole story. Analyzing glucose clamp data from 50 SFGH GCRC studies (Schambelan, Grunfeld, Lo and others) involving HIV-positive volunteers with fat distribution abnormalities ($n = 21$ on a PI, $n = 7$ not on a PI) and HIV-negative controls ($n = 22$), insulin sensitivity was found to be sharply reduced in the HIV-positive subjects whether or not they were on PI therapy. So protease inhibitor use may be a contributing factor for some subjects, but it is not the only contributing factor.

Using cross-sectional analysis of the MACS cohort (HIV-negative $n = 755$; HIV-positive $n = 533$), Brown et al. reported on comparative rates of insulin resistance by recent exposure to antiretroviral therapy (ART) class. Insulin resistance was determined by a technique called QUICKI, a formula based on measurements of fasting insulin and fasting glucose, and insulin resistance was defined as fasting insulin $>15 \mu\text{U/mL}$. For the purposes of the study, being HIV-negative was associated with 0 risk, and the risk increased with the following succession of factors: HIV-positive, non-ART; HIV-positive, NRTI only; HIV-positive, non-PI HAART; and HIV-positive, PI HAART. (Regarding the non-

ART group, Dr. Mulligan stated that only about 25% of those subjects were truly antiretroviral-naive, so inferences could not be made about the effects of HIV infection per se. She cited earlier SFGH studies that found no evidence of insulin resistance in untreated HIV infection.) Indinavir was the only PI significantly associated with insulin resistance, and none of the NNRTIs bore such an association. Among the NRTIs, both d4T and 3TC were statistically associated with insulin resistance; however, analyses were not adjusted for use of other NRTIs, so it is uncertain whether 3TC is an independent contributor or simply “along for the ride” with d4T. No one would suggest that NRTIs have the direct acute effects that are seen with PIs, but it is likely that increases in insulin resistance are mediated by changes in body habitus.

Tebas et al. reported on what happens following interruption of HAART, using secondary outcome data from the ACTG 5102 trial, in which subjects were randomized to IL-2 or no IL-2 and then went on treatment interruptions. Metabolic data did not differ by treatment assignment. A total of 47 patients discontinued HAART for periods of up to one year and experienced rapid declines in cholesterol, both LDL and HDL, and triglycerides. In contrast, there was no net change in insulin – though baseline insulin levels (on HAART) in this group were relatively low, and a decline in insulin resistance was not necessarily to be expected; glucose was likewise unchanged.

Dr. Mulligan closed with a question that, she said, she posed rhetorically at ICAAC. Given the prevalence, multifactorial nature, and apparent durability of insulin resistance in HIV-infected individuals and evidence that insulin is an important risk factor for

cardiovascular disease in the general population, is it time to consider interventions for insulin resistance, even in the absence of morphologic alterations? The audience was given this to ponder as, finally, Dr. Mulligan invited anyone who might be interested to attend next year’s Lipodystrophy Meeting in Dublin.

Investigational Antivirals and Antibiotics

Ian McNicholl gave the evening’s final remarks. He quickly covered a few of the antiviral and antibiotic agents in development. He began with information from the American Association for the Study of Liver Diseases (AASLD) meeting, which took place in Boston.

Hepatitis B/C Therapies

There was little information on hepatitis B therapies, but Dr. McNicholl mentioned entecavir, which Chang et al. demonstrated at the 2002 AASLD meeting to be effective therapy for patients failing lamivudine. Their study divided 181 patients into 4 groups (0.1, 0.5 and 1.0 mg entecavir daily or continued treatment with lamivudine 100 mg daily) for 48 weeks of treatment. Entecavir caused a 5.0 mean decrease in \log_{10} HBV DNA.

At the 2004 AASLD meeting, Gish et al. presented information on an open-label phase II study of viremivir, a ribavirin prodrug, in combination therapy for chronic hepatitis C. The study randomized 180 treatment naive patients to receive pegylated interferon alpha-2a 180 $\mu\text{g/week}$ in combination with viremivir at 400mg, 600mg, 800 mg twice daily or ribavirin 1000/1200 mg

daily. Patients were treated for either 24 weeks (genotype 2 or 3) or 48 weeks (genotype 1, 4, 5 or 6), then followed for an additional 24 weeks post-treatment. There was no significant difference between viraemidone (at any dose) and ribavirin in viral efficacy. However, the rates of hemolytic anemia, a common side effect of ribavirin, were significantly different: 0%, 2% and 11%, respectively, for the three doses of viraemidone, and 27% for ribavirin. The other adverse events were similar among the different treatment groups.

Afdhal and colleagues, at the same meeting, presented data on NM283, a hepatitis C therapy with specific activity against genotype 1. This oral HCV polymerase inhibitor was studied for safety, antiviral activity and pharmacokinetics over 15 days of treatment and 2 weeks post-treatment follow-up. The study population included both treatment-naïve subjects and previous interferon treatment failures. Doses ranged from 50 to 800 mg/day. At 800 mg/day, or dose titration 400-800 mg/day, subjects achieved a >1.0 mean log₁₀ reduction in HCV RNA. There were no serious adverse events or dose-limiting toxicities; however, mild nausea was a relatively common side effect, especially at doses ≥400 mg/day. Following this initial *in vitro* study, the same study team completed a preliminary phase 2a trial of NM283 + pegylated interferon alfa-2b in 30 treatment-naïve HCV genotype 1 patients. Patients were randomized to escalating doses (400 mg, 600 mg or 800 mg) of NM283 alone or escalating NM283 + PegIFN alfa-2b

(1 µg/kg) on days 8, 15 and 22. The combination therapy patients achieved a -2.7 mean change in log₁₀ HCV RNA from baseline, compared to a -0.7 log₁₀ change for those on NM283 alone. Nine of the 12 patients on the combination had >2 log₁₀ reductions by day 28. The investigators concluded that antiviral efficacy could be improved with NM283, especially among genotype 1 patients and previous IFN non-responders.

Antibiotics

Dr. McNicholl briefly touched on a few antibacterial agents, approved and investigational, that were mentioned at ICAAC. These included tinidazole, telithromycin, gemifloxacin, and tigecycline. Additionally, there were two investigational antifungals mentioned, posaconazole and ravuconazole.

Fosamprenavir and Nevirapine

In closing, Dr. McNicholl discussed presentations on fosamprenavir (with and without ritonavir) and nevirapine. First, DeJesus et al. found that when nevirapine is administered with fosamprenavir alone, amprenavir levels are substantially reduced; a ritonavir booster is necessary if the combination is to be given. And Shelton et al. compared 3 dosing regimens of fosamprenavir/r - 700/100 mg BID vs. 1400/100 mg BID vs. 1400/200 mg BID - with nevirapine. The 700/100 mg BID dose fared best in incidence of adverse drug reactions; at 1400/200 mg BID, LFTs increased and the amprenavir AUC was actually 18% lower than at 1400/100 mg BID. The 1400 mg dose is, in short, not recommended.

With this, Steve O'Brien rose to express thanks to Dr. McNicholl and the other presenters, the sponsors, and everyone who attended this evening's event.

The Community Consortium in turn thanks Dr. O'Brien and acknowledges the support from Auxilium, Boehringer Ingelheim, Bristol-Meyers Squibb, Gilead, Glaxo Smith Kline, Roche, Savient, Virco and Virologic that made this *Report Back from the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy* possible. Stay tuned for more educational offerings in 2005!

SMART Talk with Dr. Cal Cohen

The Community Consortium and CPMC presented an educational program and dinner entitled "Treatment: To Interrupt or Not -The SMART Answer" on Wednesday, October 27, 2004. The featured speaker was Cal Cohen, M.D., who presented the latest information on STIs and the SMART Study. After the presentation, Drs. Steven Deeks, Wally Krampf, and Harry Lampiris, along with a local SMART Study subject participated in a panel discussion focusing on the pros and cons of STIs.

Dr. Cohen began with an explanation of the SMART Study and its two-armed approach to treatment, either Drug Conservation (STI) or Viral Suppression (Continuous HAART treatment). He reviewed data on treatment interruptions and presented anecdotal information on his own SMART patients.

Dr. Cohen used a humorous, interactive approach in his talk and involved the attendees in voting on which treatment scenarios they would choose according

to the patient's clinical presentation (e.g., CD4 count, viral load, co-receptor switch, wild type virus). Is there a consensus among practitioners that balances patient health with the patient's wishes? What therapy would be appropriate? Dr. Cohen queried the room about potential combination therapies (e.g., triple nucleoside or quadruple nucleoside) and received varying responses. He mentioned an upcoming randomized study on quadruple nucleosides (trizivir plus tenofovir vs. Combivir and efavirenz) which should yield provocative results.

A vast majority of the audience indicated that they would choose a combination of two nucleosides and a non-nucleoside. There was little response to two nucleosides and an unboosted PI, even though nelfinavir has 20% of the market! There wasn't much enthusiasm for a two nucleosides and boosted PI regimen either. Nucleoside sparing therapies and creative Kaletra mono-therapy fared worst of all.

Dr. Cohen presented the case of a test patient who responds well to therapy, has a CD4 cell count of 590/mm³ with no detectable viral load and is feeling well. Can this patient, who's been on HAART for two years, take a break? What is the recommendation? Do we say stay on meds or suggest an interruption? SMART was developed to answer this fairly common question. As relatively no one suggested that a patient start therapy at a 590 CD4 cell count, why continue therapy when the patient reaches 590 on

therapy? This is the paradox that the SMART protocol hopes to answer.

Certainly one answer is to remain on therapy. CD4 counts will rise and viral loads will remain undetectable. Another answer is to take a break, monitor the patient and see how long it takes to need therapy again. The patient will go back on their regimen and, when CD4 levels rise again and viral load drops, will go off meds once again. The patient may go back and forth on this CD4 guided therapy.

Why would you delay therapy for someone with 590 CD4 cell count and why would you suggest to someone at 590 to stop therapy? The main reason is toxicity issues, such as rash, hepatitis, GI problems, and abnormal dreaming, that lead to deferral or cessation. Long-term toxicity issues such as lipodystrophy, bone metabolism worries, lipid consequences, insulin resistance with concern for glucose dysregulation and the metabolic syndrome, liver dysfunction and neuropathy also worrisome.

With HIV+ people who are not on therapy, the risk of MI is actually lower than the expected rate according to the DAD study. When therapy is introduced the rate of MIs immediately catches up, which cannot be explained. If the increase in rates is caused by lipids, which usually take decades to increase heart attack incidence, how do we explain the sudden MI rate increases? This is just another reason to be cognizant of the long-term implications of putting people on treatment.

What about the safer regimens that are lipid neutral, with no insulin problems, and no bone problems? Are there regimens that have no observable toxicity? Physicians are challenged to find known toxicities as

well as to be on the look out for new evidence of upcoming toxicity issues. There may be a new series of toxicity horror stories associated with long-term implications of treatment.

Why would patients on a safer regimen consider stopping or deferring therapy? Studies show adherence can wane over time as patients tire of taking pills. Erratic dosing can lead to resistance and cross-resistance, which for non-nucleosides may last forever. Even if there are no side effects and no problems with adherence, patients want to stop therapy because they can.

What do we advise somebody who wants to take a break? Data has accumulated over the last 4-5 years about patients who just take a break. Early small cohort studies showed that patients with 600 CD4 cells/mm³ dropped to 400 then leveled off after being off meds for 24 weeks. So the question became when do you restart therapy? Data on OIs shows that they rarely occur with CD4 counts over 200/mm³ and generally don't occur until the CD4 count drops below 150/mm³. So as long as the CD4 count remains above 250/mm³, OIs rarely occur and there's a 100 cell count buffer before risk starts. The SMART Protocol team looked at this data and said if you want to delay therapy as long as possible, then the restart point would be around 250/mm³. There is some latitude allowed clinicians based on CD4 percents. If somebody is exhibiting ARC symptoms (thrush, diarrhea, weight loss, and fevers) from untreated HIV, you should treat them. The team does not want patients on the Drug Conservation arm to get sick or become symptomatic. The purpose is to delay therapy until CD4 counts indicate that therapy is

needed. These guidelines create a safe cushion for delaying therapy and starting it at a point that will do no harm.

How do you know that starting with a CD4 count of 250/mm³ is as good as starting at 350/mm³ or higher? An Abbott cohort was treated with d4T/3TC and Kaletra (lopinavir) and monitored for the next 5 years. Patients started with CD4 cell counts ranging from 50 to 500/mm³. The results showed CD4 count increases were strikingly similar regardless of where the patient started. So CD4 reconstitution seemed independent of baseline counts.

This is not exactly like stopping therapy and restarting. The Spanish Retrogene study looked at treatment interruption to see if washing out the reservoirs of resistant virus and then restarting therapy improved your response; it did not. Patients stopped therapy at 400/mm³, lost about 120 cells to around 250/mm³, restarted therapy and within 4 months they were back to baseline. Within 6 months they were on the same CD4 count trajectory as those who never stopped at all.

This led to other randomized studies (Franco) where patients with CD4 counts of over 800/mm³ and undetectable viral loads were randomized into two arms: continue therapy or stop. The restart threshold was 400/mm³. These patients were followed for two years, and after 20 months, only 24% needed to restart. The cost of treatment in the Stop arm dropped by about \$300 per month.

What predicted how long patients were off therapy before needing to restart? The single best predictor was CD nadir. Those with CD4 nadirs above 500/mm³ when on therapy were able to be off for two years without dropping to less than 400/mm³. If the nadir was 350 – 500/mm³, then patients had almost the same two-year results as the greater than 500/mm³ group with a few patients dropping below 400/mm³. Those who nadired at 200-350/mm³ had a median time off therapy of about one year. Thus, those with higher nadirs are able to stop treatment for longer periods.

Some of the controversy with the SMART Study concerns the people with low nadirs (less than 200/mm³). Should they enter such a study? According to the data, a patient with a nadir of 200 could be off therapy for about 8 months. Some patients with low nadirs will experience rapid CD4 loss, but others will have considerable time off therapy. Stopping therapy in these patients does carry additional potential risk that their CD4 count may drop faster, but the SMART DSMB has studied CD4 trajectories and thus far low-nadir participants do well enough for the study to continue enrolling them.

Dr. Cohen continued to present clinical trial data on a number of studies (Staccato, Tibet), discussing the important issues and concerns regarding STIs. A number of studies have looked at viral load suppression and CD4 count. In one Thai study, 95% of both arms achieved viral suppression whether patients were on continuous treatment or CD4 guided STIs. This was significant in that, in poorer countries like Thailand, one can affectively treat twice as many people using treatment interruptions

Dr. Cohen, a member of the SMART Study Protocol team, presented a balanced, thought provoking program enhanced by excellent clinical references, stunning wit and impeccable logic.

The Consortium would like to thank Gilead for their sponsorship of this event.

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 95 of the 2,809 study participants.

A number of additional SMART substudies are in development. Currently we are participating in two substudies. One is evaluating the risk of HIV transmission in participants in the VS vs. the DC arm. The second substudy is

life and cost of care differences between the two arms of the trial. The three studies that are currently being developed will take advantage of the initial strategic randomization to compare the rates of development of 1) atherosclerosis, 2) anal dysplasia and 3) neurologic complications in the VS and DC arms. The Anal Dysplasia and Neurological substudies have been fully approved. We are currently awaiting the protocol team's selection of units that will conduct the study.

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/>

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/>

MDR (CPCRA 064)

The study closed to follow-up on June 30, 2004 and final closeout visits were performed by the end of August. The study has definitely set the mark for current views on managing drug resistance with STIs and the further need for evaluation of STIs in patients with significant drug resistance. All participating care providers and patients for this study deserve a big thank you for helping to make MDR the largest randomized study of its kind. To view the NEJM articles on MDR go to the following link:

http://communityconsortium.org/research/research_closed.html

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 to further enrollment on January 13, 2002. The study surpassed its target enrollment and continues to follow subjects already accrued. Stay tuned for further information to be made available as the study matures. Results from the FIRST NRTI substudy

comparing ddI/d4T to ABC/3TC as baseline nucleosides in the HAART regimen were released on May 13, 2003. Although we did not have any patients participating in this substudy, you may find the results of interest. Go to: http://communityconsortium.org/research/research_closed.html and see the section under FIRST to view the NRTI substudy results and Executive Summary documents.

LTM (CPCRA 060)

The LTM Protocol Team temporarily halted enrollment of the Antiretroviral-Naive Cohort effective June 1, 2004. The planned patient sample size of 1,000 was exceeded. Co-enrollment from qualifying protocols, such as FIRST (CPCRA 058), remains open.

To date, 3,180 patients are being followed on the LTM nationwide, including 153 from our site. We are grateful to the providers who made referrals to this study. If you have patients who might be interested in this study, please have them contact Paula Pell, R.N., at (415) 476-9554, ext. 324.

Marijuana for HIV Neuropathy (RCT)

The pilot study of smoked marijuana for patients with painful peripheral neuropathy has been 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. To date, 41 subjects have completed the RCT and 8 subjects are in screening. Eligible patients need to have persistent

pain of greater than 3/10 for the week prior to randomization. Participants are admitted for 7 days to the General Clinical Research Center at San Francisco General Hospital. After a two-day lead-in period, they are randomized to smoke one marijuana or placebo cigarette three times daily for the next five days. Individuals are compensated \$650 for completion of the study. This is our first attempt to conduct a randomized placebo-controlled trial investigating smoked cannabis. We need your patients with persistent pain from peripheral neuropathy secondary to HIV, antiviral therapy, or both. Please have potential participants contact Hector Vizoso, R.N., at 415-476-9554, ext. 366, for more information.

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

DHEA

The data analysis has been completed in our study of dehydroepiandrosterone (DHEA) and its effects on latent HIV replication and host immunity. Results are forthcoming later in the year. Thanks to everyone who referred participants to this trial!

Observational Cohort Study

The Community Consortium has an ongoing observational cohort study that involves 927 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>		927

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 hyperlipidemia in HIV-infected patients who are taking Kaletra (lopinavir/ritonavir). To date, 8 subjects have been enrolled. 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 on Kaletra 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. Eligible 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.

Volcano Vaporizer

The Community Consortium is looking for individuals to participate in another marijuana study. This study, which will enroll 18 healthy individuals, will 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. To date, 10 subjects have completed the study and 4 are in screening. Please have potential participants contact Hector Vizoso, R.N., at 415-476-9554, ext. 366, for more information.

This study is 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 www.sf aidsresearch.org.

Organ Transplants

Here is some information on the "Solid Organ Transplantation in HIV: Multi-Site Study", 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: 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.

Drs. Susan Buchbinder and Albert Liu, of the SFDPH, presented details of the trial at

the Consortium's recent '*Report Back from the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy*' meeting. The audience seemed to find the study somewhat controversial, and voiced some discomfort about discomfort with the potential for behavioral disinhibition. It was pointed out that MSM in San Francisco are already quite disinhibited, as evinced by rising STD incidence in the city. Dr. Buchbinder said that SFDPH is interested in the study for that very reason, because it captures the best data possible on the behavioral safety as well as the biological safety of PrEP. Noting that some high-risk gay men are already being given off-label TDF prescriptions, she expressed the hope that both the community and area medical providers might support this research initiative.

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