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educational offerings

TREATMENT: TO INTERRUPT OR NOT - THE SMART ANSWER

Wednesday, October 27, 2004
5:30 PM – 8:00 PM
Genentech Hall Auditorium
Mission Bay Campus – UCSF
600 16th Street @ Owens

Speaker:
Cal Cohen, M.D.

SATURDAY CME PROGRAM

“INTEGRATIVE HIV MEDICINE: CLINICAL TRIALS TO PERSONAL PERSPECTIVES”

Saturday, October 30, 2004
8:30 AM – 1:00 PM
Genentech Hall Auditorium
Mission Bay Campus – UCSF
600 16th Street @ Owens

Speakers:
Jason Tokumoto, M.D.
Lawrence Boly, M.D.
Misha Cohen, OMD
Jennifer Cocohoba, Pharm.D.
Donald Abrams, M.D.

“REPORT BACK - INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY (ICAAC)”

Wednesday, November 17, 2004
6:00 PM – 8:30 PM
Genentech Hall Auditorium
Mission Bay Campus – UCSF
600 16th Street @ Owens

Speakers:
Ian McNicholl, Pharm.D.
Michael Horberg, M.D.

upcoming conferences

44TH INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY (ICAAC)

October 30 – Nov. 2, 2004
Washington, DC
<http://www.icaac.org/index.html>

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

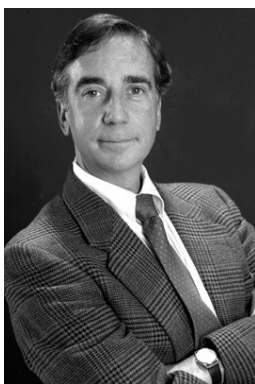
culturally diverse population desired. Please email CV to research.jobs@sfdph.org or mail to HIV Research Hiring Official, 25 Van Ness, Suite 500, San Francisco, CA 94102.

executive advisory board

The Executive Advisory Board extends a warm welcome to its newest member, Dr. Harry Lampiris.

The next meeting of the Community Consortium Executive Advisory Board is slated for October 27th. Meetings take place at 7:30 AM in the Conference room at the Community Consortium.

Happy Autumn!



Donald I. Abrams, M.D.,
Editor



Steve Murray
Guest writer

The Community Consortium presented its *Report Back From the 15th International AIDS Conference in Bangkok* on July 28, 2004, at Mission Bay's Genentech Hall Auditorium. Donald Abrams, MD, Consortium Chairman, moderated the panel of speakers which included C. Bradley Hare, MD, Assistant Clinical Professor of Medicine at the Positive Health Program, UCSF, Richard Cazen, MD, and William Owen, MD, both in private practices in San Francisco. They shared their perspectives on the conference in a round robin discussion. All agreed that these conferences have become truly international and that Bangkok provided a particularly colorful and exotic backdrop for the meeting. Many photos were interspersed with the scientific presentation slides. The panelists acknowledged that many of the slides presented were derived from the Clinical Care Options for HIV series (<http://www.clinicalcareoptions.com/hiv/vp/iac2004>)

Global Status

Donald Abrams introduced the panel and interjected his own overall impression of the meeting as being a totally global event. Holding the meeting in Thailand allowed increased exposure of the serious HIV/AIDS problem impacting that nation and much of Southeast Asia. The diversity of conference attendees continues to increase. Donald reported that UNAIDS statistics suggest that nearly 40 million people are living with HIV and that the prevalence of HIV among adults is now just over 1% worldwide. Sub-Saharan Africa still bears the bulk of the global burden with 50% of all cases. The number of new cases of HIV infection in 2003 is estimated at 4.8 million with 2.9 million deaths. Young women in many sub-Saharan African nations are infected at a rate 2-3 times higher than young men. While heterosexual sexual transmission is the major route of new infection in Africa, this varies around the world. In the U.S.,

Canada and Western Europe, men having sex with men and injection drug use are predominant. In Eastern Europe and Central Asia, injection drug use is the main risk. In India the infection is mainly sexually transmitted. In urban China, injection drug use is the risk where in rural areas contaminated plasma is a major factor.

1st Line ARV

Dr. Owen opened his remarks by also commenting on the universal flavor of the conference and touched on the presence of pharmaceutical companies and the usual protest they engendered. Generic pharmaceutical companies were also represented including GPO, whose product GPOvir is a combination of stavudine, lamivudine and nevirapine. The Prime Minister of Thailand announced that GPOvir would be sold at cost to neighboring nations.

Bill mentioned that there were not a lot of new presentations – no large studies that would alter provider practice patterns were discussed. There were, however, updated extensions of previous trials showing that agents that are in use do work over the duration, which is encouraging. For example, the Gilead 903 Study compares tenofovir and stavudine in combination with 3TC and EFV. Over 144 weeks of follow-up, both regimens remained equivalent, with very good numbers of patients continuing to have undetectable HIV RNA via an intent to treat analysis (73 and 69 % respectively). Mutations developing in the first year were mainly associated with EFV (K103N) and, to a lesser extent, M184V mutations. Seven patients developed K65R mutations. In the subsequent follow-up, fewer mutations were recorded overall.

Dr. Owen reviewed information on rescue therapies in 8 patients who had developed K65R mutations. Five of the eight were able to achieve HIV RNA levels < 50 copies/mL with the use of boosted PI regimens. Some of the successful regimens actually contained tenofovir despite the K65R mutation, which, along with phenotypic results, implies that the virus remains sensitive to the drug even with the presence of the K65R mutation.

He then reviewed the extended data on DP-006, which had established the combination of AZT/3TC/EFV as being a first-line treatment of choice. With 168 weeks of follow-up available, the regimen remains

superior to the comparator arms of EFV/IDV and AZT/3TC/IDV with regard to viral suppression. Final data was presented on the Class Study, which looked at the combination of 3TC and abacavir used in combination with either boosted amprenavir or stavudine or efavirenz. While it was reported previously that the EFV arm seemed to be better than the other two arms out to one year, after 96 weeks there was no statistical difference among the three regimens in the intent to treat analysis.

The Solo Study evaluated boosted fosamprenavir vs. nelfinavir after 48 weeks and found similar efficacy with regard to decreasing HIV RNA to < 400 or <50 copies/mL. In the subset of participants with high viral load and low CD4+ cell counts there was a difference between the fAPV/r and the NFV with, respectively, 74% vs. 44% achieving < 400 copies/mL (< 50 copies/mL 51% vs 33%). There were also fewer mutations in this subset in the patients receiving fAPV/r compared to NFV.

Prognosis after starting HAART

Dr. Hare was somewhat less jaded and more enthusiastic and positive about the Bangkok meeting than his elder, or shall we say more senior, colleagues. He felt that the international mix of presenters was a real plus and that it was nice to see researchers from less developed nations being able to present their data to an international body of peers.

Dr. Hare began his presentation of data by reviewing a San Francisco based study where the investigators evaluated the association between the WHO ‘3 x 5’ regimens and survival. The World Health Organization has an initiative to treat 3 million people by 2005. They have

established 4 standardized treatment regimens that use nucleoside backbones of d4T/3TC or AZT/3TC in combination with an NNRTI (NVP or EFV). This retrospective case-controlled study looked at 310 AIDS cases in San Francisco (where the patients had died) and matched those to 1161 controls. All patients had started a HAART regimen between 1996 and 2003. They compared all the initial HAART regimens employed and investigated which were associated with the best survival. It was encouraging to those who support the WHO initiative to see that those 4 regimens performed the best compared to other regimens. Dr. Hare pointed out some important caveats to this study: there was very little boosted PI use and it looked at an experience where alternative and second-line therapies were available as opposed to the current situation in many developing nations.

The ART Cohort Collaboration looked at an analysis of 12 different cohorts in the US and Europe, involving nearly 20,000 patients, to investigate the prognosis after initiating 3-drug HAART regimens. This study included over 55,000 person years of follow-up. Between the years of 1995 and 1998, there was a significant decline in both AIDS and death, but there was really not much change between 1998 and 2003. In fact, in some of the cohorts there was actually an increase in the death rate between 1998 and 2003. However, investigators did see an increase in the proportion of patients with undetectable viral loads in these cohorts over time continuing through 2003. The predictors of progression and death, not surprisingly, were low CD4, older age, a history of injection drug use, CDC stage C disease and low hemoglobin at baseline. There was only a weak association with viral loads. A

possible explanation for lack of further improvement in prognosis was aging of the cohorts as well as comorbidities and treatment failures in IDUs.

An analysis of EuroSIDA data investigated regimens associated with increased risk of viral rebound. The investigators evaluated 1,951 patients with no detectable viral load (<50 copies/ml) who had not virologically failed a previous regimen. They defined viral rebound as viral load >400 copies/ml on two consecutive occasions. They stratified by patients who were naive prior to HAART and patients who had NRTI experience prior to HAART. Among those who were naive, the overall rate of rebound was about 5 per 100 person years of followup. The lowest rate of rebound was with the EFV based regimens at 3.1/100 PY; nelfinavir- based regimens had a rebound rate that was significantly higher, at 8/100 PY of follow-up. Interestingly, in these naive patients, the triple nucleoside combinations which included abacavir were not statistically different from the EFV based.

Dr. Hare concluded his first round of comments by updating Abbott 720. Of the remaining participants in this five-year study of 3TC, d4T and lopinavir/r, two-thirds continue to have undetectable HIV RNA. Of the 27 patients undergoing resistance testing (16 patients with loss of virologic response and 11 patients who had one or more “blips”), there were 17 successful genotype results. Absolutely no lopinavir or stavudine resistance was detected. Only three of the 17 had 3TC resistance. Another abstract presented a smaller Abbott study looking at BID vs. QD

LPV/r in combination with tenofovir and FTC in a naïve population. Of the 8 patients who failed on the QD arm and the 7 who failed on the BID arm on this study, none demonstrated resistance to either LPV/r or TNF. Three patients were resistant to FTC.

Metabolic Complications

Dr. Cazen opened his remarks by saying that he found it astounding that 20,000 people attended the conference, including the Third World participants and the Global Village. On the other hand, he agreed that the science was not exactly earth shattering, but felt that there were some interesting developments in the metabolic area.

Dr. Cazen turned to the CPCRA FIRST study, investigating backbone nucleoside analogs with either an NNRTI or a PI or a combination of a PI and an NNRTI in naïve patients. In the NRTI substudy, 180 patients were randomized to receive either ABC/3TC or d4T/ddI. Body composition and metabolic data in both groups over 32 months were analyzed. Between months 1 and 12, there were increases in body cell mass and fat in both arms of the study, which is consistent with just about every study where patients are treated for HIV. Their general health and nutrition improves and they put on fat and body cell mass. But there was divergence after month 12 to the end of the study at month 32. Total and regional fat in the d4T/ddI cohort diminished as compared to the ABC/3TC group by a statistically significant degree. One of the limitations of this study was that DEXA and CT scanning were not used. The investigators did use anthropometrics which provide pretty reliable data, but it would have been better if they had used other tools. There was also statistically

significant worsening of the HDL and triglycerides in the d4T/ddI arm.

Dr. Cazen next reported on a study investigating mitochondrial DNA in fat biopsies. Past studies have shown diminution of mtDNA in fat biopsies taken from both areas of lipohypertrophy and lipoatrophy in patients on thymidine analogs, particularly d4T. In this study they did fat biopsies and also looked at the peripheral blood mononuclear cell (PBMC) mtDNA levels in patients on an NRTI-sparing regimen. The patients all received IDV/r and EFV for 48 weeks, after which they underwent fat biopsy from the inner thigh and the PBMC studies. They found a significant increase in the mtDNA in the fat biopsy as well as a smaller but more statistically significant increase in the PMBC. However, when the results were stratified for previous NRTI use, the fat mtDNA recovery was only significant with a switch from d4T and the increase in the PBMC mtDNA was only significant with a switch from AZT, not d4T. Interestingly, none of these changes correlated with any regional fat changes. Again, it is the same old situation that although mitochondrial toxicity of nucleosides has been implicated in the lipodystrophy syndrome, particularly in lipoatrophy, it has not been totally proven. Dr. Cazen reported that this is another study where you see the changes that may be an epiphenomenon from the change in the drug, rather than a causative agent.

The BMS-034 study originally looked at atazanavir vs. EFV. The efficacy data had been presented in the past and remain controversial. Dr. Cazen described the 48-week total body fat changes as measured by DEXA in the

study. After 48 weeks, body fat increased somewhat in each group, but there was little significant difference between the two arms. The appendicular fat, likewise, had a very minimal change overall and little change between the two groups. The analysis of abdominal fat, further broken into subcutaneous adipose tissue vs. visceral adipose tissue, there was an increase in the subcutaneous tissue in both groups and likewise the visceral adipose tissue had an increase over the 48-week period, but again not particularly different between the groups. Interestingly, people that were underweight to begin with put on the most fat. People who had normal insulin resistance put on more visceral fat and the people who were over the age of 40 tended to put on more visceral fat, coinciding with previous study results. The bottom line is that fat gain thought to be a restoration to health is not different between the EFV and ATV groups.

The GS 903 study compared TDF/3TC/EFV and d4T/3TC/EFV. Total limb fat at week 144 was compared; unfortunately the investigators only began to collect the data at week 96. In the stavudine cohort, the limb fat is significantly lower at the initial week 96 determination compared to the TDF group. Over the next 48 weeks there was an increase in total limb fat in the TDF group and a further decrease in the d4T group. The limb fat in women plateaued out over the 48-week period in the TDF arm and there was a very slight decrease in the d4T arm. There was a statistically significant difference

between the two arms with lower limb fat seen in the stavudine group at week 96 and 144. Men tended to have lower limb fat to begin with, and had a similar diminution of limb fat in the d4T group as compared to the TDF group. The TDF groups had about the same limb fat in men as the d4T group had in the women.

Dr. Cazen went on to describe the metabolic findings from an induction-maintenance approach. Patients who were naive to antiretroviral therapy received trizivir and EFV for 48 weeks and then if they fully suppressed (HIV RNA < 50 copies/mL) they were randomized to continue the same therapy or continue TZV alone. These patients did maintain full viral suppression during the 96-week period and there was a significant improvement in lipids, with a marked reduction in the cholesterol, LDL and triglycerides in the patients who eliminated the EFV.

The 2NN Study was concluded after 48 weeks looking at viral efficacy of regimens containing NVP, EFV or both added to ddi/d4T. Dr. Cazen reported on the extension of the study, looking at lipid data on 320 patients who continued beyond the 48 weeks. The bottom line is that if you look at the triglycerides, after week 48 to a mean of week 84, they continue to rise, both in the NVP and the EFV arms. The combination of the two is additive.

In another metabolic study, tenofovir was substituted for a PI or an NNRTI with follow-up over a 48-week period. Following the substitution, there was an improvement in lipids (LDL, TC, and TG) in the patients switched to TDF. None of these patients lost viral suppression. Although Dr. Cazen cautioned that changing to an all nucleoside regimen is not necessarily the best therapy from a virologic point of view, this study does

demonstrate improvement in lipids when TDF replaces the NNRTI or PI in a regimen.

There was little data presented on pharmacologic therapies of body habitus alteration, but Dr. Cazen did report on the results of a study investigating the anabolic steroid oxandrolone as a treatment for lipodystrophy, particularly visceral fat accumulation. While oxandrolone did result in a statistically significant increase in body cell mass and a trend towards loss of total fat, subcutaneous abdominal fat and visceral abdominal fat as compared to the placebo group, it did have a deleterious effect on the lipids, particularly the HDL and to a lesser extent, the triglycerides. Dr. Cazen advised that providers should cycle oxandrolone and not use it continuously.

STI Data

After the 2002 Barcelona Conference, “half the world was clamoring to get on antiretrovirals, and the other half was clamoring to get off of them” according to a piece written by Abigail Zuger, MD, for the NY Times. At the Bangkok meeting there seemed to be fewer presentations on STIs. Dr. Abrams reviewed the rationale for use of STIs in the treatment of HIV infection. An STI could possibly serve as an auto-immunizer to boost HIV specific immune responses. Jay Levy, for example, has always felt that if the viral load is suppressed fully all the time, we may be eliminating some of the body’s own immune function against HIV. Allowing some level of viremia, patients may benefit from cell-mediated immunity. For people who have used up their options with regard to the development of multi-drug resistant virus, it was felt that treatment

interruption might allow re-population by wild-type virus that could be more susceptible to reintroduction of therapy; however, the MDR Study (CPCRA 064) did not show any real clinical benefit in this setting. Reducing overall drug exposure, especially in patients with relatively high CD4 counts, who may not even have needed to be put on antiretroviral therapy in the current iteration of treatment guidelines, reducing adverse experience and cost, and perhaps improving quality of life, are other rationales for treatment interruptions.

Donald reported that CD4-guided treatment interruptions are gaining more favor than those that are time driven. That was borne out by the small Stacatto study from HIV-NAT. Patients with CD4 cell count > 350, undetectable viral load for more than six months, on two nucleosides and SQV/r were randomized either to continue HAART or to use CD4-guided HAART so that they maintained counts in a certain range similar to the SMART study. The third group was one week on, one week off of HAART therapy. The primary endpoint was the percentage of patients who had viral loads < 50 copies/mL. There were no virologic failures in the group that got continuous antiretroviral therapy and only 1 person failed with the CD4-guided STI. However, in the third arm 50% of the patients did fail. CD4+ cell counts >350 at week 108 were similar in the group that had the continuous therapy compared to

the group that had the CD4-guided interruptions.

There was a discussion of patient preferences after participating in the trial. They were asked to choose whether they wanted the continuous HAART or CD4-guided interrupted therapy. Two thirds chose continuous therapy citing fear of developing illness, developing resistance, or low levels of CD4.

There was a commonality of findings with regards to CD4-guided interruption factors that seemed to be associated with the duration of time that patients can remain off therapy: baseline and nadir CD4, lower pre-HAART viral load and the absolute duration of prior virologic suppression. A substantial proportion of patients on these studies are able to remain off therapy for prolonged periods. The SMART data presented by Wafaa El-Sadr show that up to 50% of patients are maintaining CD4 cell counts > 250 cells/mm³ during 48 to 96 weeks off therapy. An ACTG study that looked at Interleukin-2 plus HAART vs. HAART alone prior to the treatment interruption showed no significant difference in the proportion that were able to remain off therapy at 48 weeks.

There are issues such as the longer half-life of NNRTIs and how to safely interrupt therapy in patients who are on NNRTI-based regimens, consequences of viral replication once the treatment is stopped, whether people get the acute retroviral syndrome, effects on their nervous systems, immunopathogenesis, and increased risk of HIV transmission that need to be addressed in patients using the strategy of structured treatment interruption. Some of these questions will be answered by the SMART Study (CPCRA 065). If you are interested in learning more about the whys and

wherefores of treatment interruptions and particularly the SMART study, please join us on October 27 for a presentation by Cal Cohen, MD, of the New England CRI and the SMART Protocol Team!

New Antiretrovirals

Bill Owen returned to the podium to discuss information presented in Bangkok on some of the new antiretroviral therapies. He reported on the Boehringer-Ingelheim open-label study looking at their PI, tripanavir, in 296 highly PI-resistant patients. All participants had at least three baseline PI-related mutations at codons 33, 82 and 84 and/or 90. They were randomized to receive either boosted lopinavir, boosted amprenavir, boosted saquinavir or boosted tripanavir for the first two weeks. The other groups all added TPV/r after the initial two weeks of therapy. The added TPV/r had an HIV RNA effect but it was short-lived, lasting about 4 weeks. Drug levels of the other PIs were markedly reduced with TPV inducing metabolism of these second PIs. Dr. Own cautioned that we must be aware of the deleterious effect of combining tripanavir with other PIs. More pharmacokinetic data is needed before combinations are utilized.

Bill felt that, from a clinician's perspective, the absence of information on new nucleoside analogs was disturbing. One new NRTI in development is D-d4FC or Reverset. The drug was initially investigated in treatment naive patients where a 1.8 log₁₀ decline in HIV RNA was achieved. In treatment-experienced patients, the decrease was not as robust (0.8 log₁₀)

using Reverset as a monotherapy over a ten-day period.

The UK-427, 857 Study from Pfizer looked at various dosing regimens (once a day, twice a day) and with fasting and fed states using this novel CCR5 inhibitor. They found that bioavailability is reduced with food, but there is no decrease in anti-viral activity. Other CCR5 inhibitor *in vitro* studies were presented. GSK has 873140, which had difficulty selecting resistance in serial passage. One of the concerns was that there might be a switch to the other co-receptor CXCR4, but there was no evidence of this in these *in vitro* studies.

Several novel applications for tenofovir were presented as well. Studies of TDF for protection from oral SIV transmission in infant macaques and TDF prophylaxis against HIV acquisition from breast milk were encouraging. Safety and tolerability was studied for a TDF vaginal gel as well as TDF as a pre-exposure prophylaxis.

Management of Experienced Patients

Brad Hare returned with comments about studies focused on HIV-experienced patients. The CONTEXT Study enrolled patients who had failed previous regimens (one or two PIs). The trial compared once a day fos-amprenavir, twice a day fos-amprenavir (both boosted) and lopinavir/r. The fAPV/r once daily arm was inferior to the comparator arms. The twice-daily fAPV/r failed to meet the

noninferiority endpoint, but was not proven to be inferior either. Both drugs showed similar decreased efficacy with baseline mutations: M46IL (50%), L90M (52-61%), V82A/F/T/S (22-35%), and I84V (17-40%).

The TORO studies were the registration trials for enfuvirtide, T20. Primary endpoints for these studies were at week 24 with data now available to week 96. Those who continued T20 maintained very high levels of viral suppression as well as CD4 increases. No new safety concerns were identified. Information on resistance to enfuvirtide, specifically at gp41, was reiterated. Resistance occurred mainly within the 'hotspot' between codons 36 and 45. They did also identify other codons outside this range that had lower levels of mutations associated with resistance.

A small but important study examined the development of resistance mutations in the presence of low-level viremia. The study evaluated twenty-two patients who had at least two genotypes while their viral loads were between 50 and 1000 copies/mL and who underwent no change in their regimen. Fifteen of the 22 developed new mutations during the median 28 months between tests while maintaining stable CD4+ cell counts and HIV RNA levels. M184V, K65R and TAMs were the most frequent mutations (10 patients were on triple nucleosides, 8 on PI and 4 on NNRTI-containing regimens). The investigators concluded that in the presence of ongoing replication, even with low-level viremia, new mutations are accumulating. This may support early switching when other options exist to minimize accumulation of mutations, subsequent viral rebound, and decreased treatment options.

HIV Transmission

Dr. Hare next discussed some data on HIV transmission which emerged from the local Options Project in which he is a co-investigator. Options is a local observational cohort study of acute and early HIV infections. An Options poster at the conference looked at transmission of drug resistant virus. It had been postulated that drug-resistant virus may not be easily transmitted. This analysis however, did not support that conclusion. Forty-seven partner pairs where transmission occurred were followed and most resistant mutations in the source partner were found in the newly infected partner.

The Positive Partners study is another prospective San Francisco cohort of serconcordant HIV-positive partners and individuals who engage in unprotected anal or vaginal intercourse. At baseline all partner pairs had different viruses detected through phylogenetic sequencing showing no evidence of transmission linkage. After 59 person years of follow-up and 3725 cases of unprotected exposures, no superinfections were found among the chronically HIV-infected. One potential case of superinfection in a recent seroconverter is still being evaluated. This highlights the fact that superinfection occurs primarily among individuals who acquire it in early or acute HIV infection. Among chronic infection superinfection appears to be very uncommon.

A southern California group described three cases of superinfection among patients not on antiretroviral therapy. This was detected through genotypic resistance testing (wild type to resistant and vice versa). Superinfected patients

experienced increased viral loads and decreased CD4+ cell counts indicating potentially bad clinical outcomes. In Tanzania, where there are multiple clades of HIV circulating, 28% of those studied had dual infection with more than one clade detectable over time. Finally, another study of long-term exposed individuals showed that many had a different virus than their seropositive partners. The investigators propose that long-term exposure to their partners' virus may elicit a protective response to similar viruses, but not to divergent viruses. This may explain why superinfection is rare among populations with relatively homogenous virus (US) where higher rates exist in variable virus areas (Africa).

Maternal to Child Transmission

Studies confirming the development of resistance using single dose nevirapine to prevent MTCT were presented. The new data reinforced prior findings of a 25-75% rate of development of resistant virus as well as supporting a new strategy of administering NVP to the infant only as a means to prevent or decrease MTCT. Another new treatment was the use of single-dose NVP with a tail of Combivir to protect against resistance to both mother and baby. Resistance was 50% among mothers who got single-dose NVP and reduced to 5-13% when this tail of AZT/3TC was added.

Safety of Tenofovir DF

Dr. Cazen reported on a collation of data from studies on the renal safety of TDF ranging from 48 weeks to 3 years. There was little evidence of progressive renal dysfunction in patients with normal renal function at baseline, and only a very slight decrease in renal function by very sensitive measures, despite no change in creatinine clearance, could be detected. In 144-week data from the 903 study, there was no convincing evidence of changes in creatinine or phosphorus seen between the arms. The only studies that did show some renal dysfunction in TDF recipients were in patients who were on other nephrotoxic agents as well. The best advice, per Dr. Cazen, is to avoid TDF or use it with very careful monitoring in patients who have pre-existing renal disease.

Other Complications

Dr. Cazen reported on some other complications of HIV infection that were described. One study determined that gynecomastia, while rare (3%), was probably related to hypogonadism. The rates were similar to the general population. Other contributing factors were lipoatrophy and hepatitis C infection. A very interesting presentation on preeclampsia was given where HIV infection seemed to be an independent risk factor for preeclampsia and infant death. It appears related to the chronic maternal use of antiretrovirals before pregnancy.

A French study reported a significant relationship between duration of exposure to antiretroviral therapy and development of osteonecrosis. There was also some association with CD4+ cell count. Prior to this it was not clear that ARV therapy had any relationship to the development of

osteonecrosis. Another study looked at bone mineral density in patients on TDF vs. d4T in women on the 903 study. There was a statistically significant decrease in bone mineral density on the TDF arm. The results in men are not as dramatic, but mirror the women's rates. The BMD decline is seen for both hip and spine measurements. This all translates into only a very low rate of fractures to date: 1% in the TDF/3TC/EFV arm and 4% in the d4T/3TC/EFV arm.

Dr. Cazen finally showed slides of the skin discoloration seen in patients receiving FTC. The discoloration, while mild, occurred mainly on the palms and soles and most frequently in African Americans. The effect was seen in 2 – 6 % of patients in FTC Phase 3 trials. The key point is that the discoloration presents as dark spots on the palms and soles, similar to secondary syphilis. The median time to onset of the discoloration is 70-90 days after beginning treatment. There was no association with dermatologic or systemic conditions and in some cases it was reversible on discontinuation of FTC.

Pharmacology

Dr. Hare returned to discuss some pharmacology issues. He turned first to the report on the pharmacogenomics of nevirapine hypersensitivity. The same group that previously reported an allele associated with abacavir hypersensitivity now describes HLA-DRB1*0101 as a genotype associated with a higher risk of hepatitis and/or rash and fever in patients receiving NVP. The positive predictive value was only 40% but the negative predictive value was 94%, suggesting that in the future one may be able to use

pharmacogenomics to select patients for whom NVP would not likely precipitate these reactions.

Another important pharmacology issue is the concern that protease inhibitor levels may be decreased during the third trimester of pregnancy. The Pediatric ACTG found that women in weeks 30-36 of pregnancy had lower lopinavir levels than would be expected from historical controls. Although postpartum the lopinavir levels rose, they were still lower than expected. Although the majority of women maintained virologic control, the PACTG has launched a new study to investigate higher doses of LPV/r in the third trimester in an attempt to achieve lopinavir levels that are closer to the non-pregnant historical controls.

Dr. Hare reported that one of the big stories of 2003 was the failure of some of the triple nucleoside regimens, particularly the once a day regimens that included abacavir, tenofovir, and 3TC. One hypothesis was that there might be a potential intracellular interaction between ABC and TDF leading to a lower concentration of one or both drugs. This hypothesis has been ruled out by a number of investigations reported at the Bangkok meeting. The most likely cause of failure may be the low genetic barrier to resistance in the combination.

HCV/HBV/HPV

Dr. Cazen closed the evening by discussing issues of HCV coinfection and information on opportunistic infections. A number of studies at the meeting suggested

that HCV coinfection was associated with higher rates of mortality, even in the HAART era. This was supported by a large VA cohort study where a 38% increase in mortality was seen in coinfecting patients. However, a CDC analysis showing increased mortality in HCV+ patients, when corrected for alcohol use, IV drug use, and HBV, found no difference in survival between HCV+ and HCV- patients.

Another study looked at both HCV+ and HCV- patients on HAART to determine whether there was blunting of the CD4+ cell response in coinfecting patients. The mean increase in CD4+ cell count after 3-12 months on HAART was compared. There was not as robust a rise in CD4+ cell counts in the HCV+ patients. Patients who initiated HAART in 2001-2003 had a blunted CD4 cell count as compared to those patients who started HAART in 1998-2000. Coinfecting patients with more advanced HIV disease at baseline also had a markedly increased risk of having a blunted CD4+ cell response.

Dr. Cazen discussed two studies investigating the use of boosted lopinavir in coinfecting patients. Of 819 patients in LPV/r studies, the HBV/HCV+ coinfecting patients ($n=132$) were more likely to have grade 3/4 elevated liver functions tests (13% vs 3% in non-coinfecting controls). This was not specific to LPV/r; in fact there were fewer elevations in the LPV/r than the nelfinavir group. In a Canadian retrospective chart review, 21% of hepatitis/HIV-coinfecting patients initiating HAART experienced grade 3/4 elevations of liver function tests. In this analysis, age and current LPV/r were the major risk factors. Overall, Dr. Cazen suggests that LPV/r should be used carefully in coinfecting patients. Other PIs and NNRTIs

should be carefully monitored in coinfecting patients as well.

Predictors of response to peginterferon/ribavirin therapy for HCV were reviewed. The predictors turned out to be HCV related and not HIV related. Baseline CD4 counts, viral load, use of ARV therapy and type of ARV therapy were not significant predictors. The genotype (non-1 vs 1) and the HCV viral load were the two major predictors of response. Low CD4 cell count had been seen as a barrier to treatment of HIV/HCV coinfecting patients with interferon-based therapy. This may not be true; patients with CD4+ cell counts <200 may have a reasonable chance to respond.

With the widespread use of lamivudine, there has been a concern of an increased risk of lamivudine resistant hepatitis B virus. A French study investigated the use of adefovir in patients with 3TC-resistant HBV. After 192 weeks of treatment with adefovir, 59% had reached undetectable HBV viral loads and 70% had normalized their liver functions tests. They had an excellent response to low dose adefovir without evidence of nephrotoxicity or other toxicities. There was no emergence of the K65R mutation or the adefovir resistance mutation at codon 70. There was also an improvement in fibrosis seen with increasing numbers responding at week 192 (50%) compared to week 48 (33%).

Dr. Cazen concluded with a report of another local trial that he felt had significant clinical impact. Tony Lee, MD, and colleagues at San Francisco General Hospital had an oral presentation describing results from PAP screening for anal dysplasia. In this prospective

study, 417 men seen in the Positive Health Practice at SFGH underwent biannual anal PAP smear screening. Fifty-four percent were positive on PAP smear. All positive PAPs were followed by high-resolution anoscopy. Four (1% total screened) were found to have biopsy-proven anal cancer (all *in-situ*). The initial PAP had high sensitivity (95%) but low specificity (34%). The appropriate treatment of anal dysplasia and benefits of early treatment remain unclear.

The Community Consortium is grateful to: Agouron, Boehringer-Ingelheim, Bristol-Meyer Squibb, Gilead, GlaxoSmithKline, Roche, Savient Pharmaceuticals, Tibotec, and ViroLogic for their unrestricted educational grants which made this Report Back from Bangkok possible!

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 87 of the 2214 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 investigating quality of 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 over a year ago, 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-enrollments 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, 37 subjects have completed the RCT. 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.cmcrc.ucsd.edu/>).

DHEA

We recently completed followup of our study of dehydroepiandrosterone (DHEA) and its effects on latent HIV replication and host immunity. Data will be analyzed and results 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 has begun enrollment on 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). The mushrooms are administered as a freeze-dried powder in individual 15-gram packets, which are added to soup packets or other foods and taken once a day. The study is open to individuals who have been on Kaletra for ≥ 12 weeks and who have non-HDL cholesterol levels ≥ 160 mg/dL; 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 will be followed at the General Clinical Research Center (GCRC) at San Francisco General Hospital. They will have two overnight inpatient visits and three outpatient visits there over the course of the study. Visits will involve completing questionnaires and having blood drawn; inpatient visits will 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. . 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.

Sculptra Approved

(reprinted from an online AEGiS article <http://www.aegis.org/news/fda/2004/FD040802.html>)

The Food and Drug Administration, approved Sculptra, an injectable filler to correct facial fat loss in people with human immunodeficiency virus (HIV) on August 3, 2004.

Sculptra is the first such treatment approved for a condition known as lipoatrophy, or facial wasting, a sinking of the cheek, eye and temple areas of the face caused by the loss of fat tissue under the skin which can affect HIV patients. FDA expedited review of the product because of its importance in treating people living with AIDS.

Sculptra is an injectable form of poly-L-lactic acid, a biodegradable, biocompatible synthetic polymer from the alpha-hydroxy-acid family that has been widely used for many years in dissolvable stitches, bone screws and facial implants. FDA approval of Sculptra was based on data from four studies, totaling 277 HIV-positive patients with severe facial lipoatrophy. The patients, who were all being treated with antiretroviral drugs, were primarily white males, mostly ages 41 to 45. Patients were given three to six injections of Sculptra at two-week intervals and were followed for two years.

Skin thickness measurements and serial photographs from clinical studies were assessed, as well as other data submitted by the manufacturer, Dermik Laboratories, of Berwyn, Pa. Analysis indicated that the product significantly improved facial appearance, and was safe for restoration and/or correction of shape and contour deficiencies resulting from facial fat loss in patients with HIV/AIDS. Sculptra was shown to produce significant increases in dermal thickness (up to 2 to 3 times baseline values), adding volume to facial tissue and restoring

shape to areas of the face with fat loss.

After an initial treatment series, repeat treatments may be needed to maintain the correction. Most adverse events were related to the injection itself and included nodules, redness, swelling and bruising in the injection area.

The studies also demonstrated significant improvement in quality of life, and measures of anxiety and depression, conditions which can be associated with lipoatrophy.

Sculptra should only be used in patients with HIV by health care providers who are fully familiar with the product training materials provided by Dermik and the entire product package insert. The use of the product for other indications, such as to treat wrinkles, has not been approved by FDA.

Sculptra should not be used in anyone who is allergic to any of the product's components. As a condition of approval, Dermik has agreed to conduct an open-label registry study of 100 patients for five years to evaluate Sculptra's long-term safety. The study will include at least 30 females and 30 people with dark skin types.

IN MEMORIAM...

*Nicholas Burik, M.D.
Mauricio Flores
Keian Kunkler
Neil Monello*

Dr. Nicholas Burik passed away suddenly at his home on August 15 at the age of 66. Dr. Burik was a longtime member of the Community Consortium and a staff member of St. Mary's Hospital and Seton Medical Center.

Keian Kunkler, former Community Consortium CAB member and CCG alternate, passed away suddenly on August 8th. He was 40 years old. Keian represented the Community Consortium by attending the CPCRA Winter and Spring Group meetings in 2002 and 2003.

Neil Monello, Community Consortium CAB member passed away on July 31st. He was also a member of UCSF AIDS Clinical Trials Group and participated in various clinical trials as well.

Mauricio Flores Mendoza, beloved partner of the Community Consortium's Pierre-Cedric Crouch, died at his home on February 16, 2004 due to acute renal failure and complications of AIDS. He was 37 and served as the Community Consortium's CCG alternate.

Autumn 2004

**Are you HIV-positive?
Are you taking Kaletra?
Is your blood cholesterol level too high?**

You may qualify to participate in a study.

The Community Consortium is seeking HIV-positive individuals for a study of **oyster mushrooms** in the treatment of elevated blood cholesterol due to Kaletra, a protease inhibitor. The study's purpose is to see if treatment with oyster mushrooms is safe and effective when combined with Kaletra.

If you participate in the study you will

- Take oyster mushrooms, which are in the form of a freeze-dried powder, once each day for 8 weeks. Each dose is placed in an individual packet, which you will add to a soup mix or other food.
- Have 2 overnight inpatient visits at the General Clinical Research Center (GCRC) at San Francisco General Hospital, lasting approximately 24 hours each. The nursing staff will collect blood from you several times over the course of 12 hours. You will be asked to complete questionnaires and you will meet with a dietician.
- Have, additionally, 3 brief outpatient study visits at the GCRC, at which your blood will be drawn and you will be asked to complete questionnaires.
- Be reimbursed \$25 for each study visit, including the screening visit, and an added \$50 for each overnight stay at the GCRC; you will receive \$50 reimbursement for completion of the study. The total reimbursement, if you finish the study, is \$300. Reimbursement will be given at each visit.

This study is open to HIV+ people who

- Have been on Kaletra for at least 12 weeks.
- Have a non-HDL cholesterol level of at least 160 mg/dL and normal liver function tests within 30 days prior to starting the study.
- Are not currently taking any cholesterol-lowering treatments, and have not had abnormal muscle conditions caused by such treatments.
- Have not been diagnosed with rhabdomyolysis or diabetes mellitus.
- Are not pregnant or breast-feeding.
- Meet other criteria as required by the study.

For more information, call (415) 476-9554, ext. 315.

Community Consortium

UCSF Positive Health Program at San Francisco General Hospital