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educational offerings

“Report Back from International AIDS Conference” Bangkok, Thailand

Wednesday, July 28, 2004

At our new location:

Genentech Hall Auditorium

UCSF - Mission Bay Campus

6:00 PM – 8:30 PM

Details to follow....

upcoming conferences

15TH INTERNATIONAL AIDS CONFERENCE

JULY 11-16, 2004

BANGKOK, THAILAND

[HTTP://WWW.IAS.SE/](http://www.ias.se/)

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

OCTOBER 30 – NOV. 2, 2004

WASHINGTON, DC

[HTTP://WWW.ICAAC.ORG/INDEX.HTML](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.**

welcome to sharon o'leary, r.n.

Sharon O'Leary, RN, BSN, CRCC, came from the Independent Clinical Trials Group at UCSF PHP in December 2003. In her position at the ICTG Sharon supervised NIH and CDC sponsored as well as industry sponsored and investigator initiated clinical trials for persons with HIV or at high risk of exposure to HIV.

Sharon brings over 11 years of experience as a clinical research nurse coordinating primarily HIV and Hepatitis C research at UCSF, Stanford University, and the AIDS Community Research Consortium (ACRC).

Sharon is a Certified Clinical Research Coordinator (CCRC) and a member of both the Association of Clinical Research Professionals (ACRP) and the Association of Nurses in AIDS Care (ANAC).

membership renewal

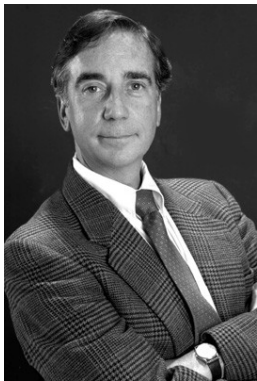
If you haven't already renewed, we once again seek your support to assist us in the work that we do for HIV care providers in the Bay Area and beyond. We appreciate the fact that there are many competing demands and requests for our ever shrinking resources, but we hope you will continue to be able to renew your Consortium membership to allow us to accomplish our goals and better serve your needs. We need to keep an accurate updated list of individuals interested in learning of Community Consortium activities, following our research

Endeavors, and gleaning whatever gossipy tidbits *Synopsis* may otherwise have to offer. To this end, we ask for you to send back a membership application with the nominal fee that helps us with the printing and mailing of *Synopsis* and some of our other educational brochure materials. In addition, we have always claimed that our strength is in our numbers. When the Consortium takes a stance on an issue and, for example, writes a letter to an elected official, it behooves us to say that we are an organization of 200 plus HIV care providers in the San Francisco Bay Area. Obviously, the larger the number that fills in the blank, the more clout we have. The Community Consortium has much to be proud of. We have served as an ongoing model for community based clinical trials and provider education in the country. We intend to continue our efforts for as long as they are necessary. We do need and appreciate your support! Please take a moment now to fill out and send back the enclosed membership application. We know there are more providers out there who would be interested in our programs, so feel free to copy your form and share with colleagues! Thanks again for your continued support!

executive advisory board

Meetings of the Community Consortium Executive Advisory Board are slated for April 28th, July 28th, and October 27th in 2004. Meetings take place at 7:30 AM in the Conference room at the Community Consortium.

Happy Spring!



Donald I. Abrams, M.D.,
Editor



Paul Couey, CRC
Guest writer

The Community Consortium presented its annual *Report Back From CROI* on February 24, 2004, to an overflow audience at CPMC-Davies Medical Center. The program was ably moderated by Steve O'Brien, MD, Co-Director of the East Bay AIDS Center, and the panel of speakers included Stephen Follansbee, MD, Director of Kaiser HIV Services, Diane Havlir, MD, Director of the UCSF Positive Health Program at San Francisco General Hospital, and Steven Deeks, MD, also from the Positive Health Program.

Dr. Follansbee: Vaccine efficacy, surgical outcomes

Prior to his scientific presentation, Steve Follansbee took a moment to share with those present the Community Consortium Executive Advisory Board's stance on ritonavir pricing and Abbott Laboratories. A letter, sent to Abbott earlier by the Board and copied to Consortium members, explained the Consortium's response to what Dr. Follansbee termed "an act of extraordinary corporate greed." He noted that several physicians and activists had met with Abbott to voice their complaints and had not been satisfied with the company's reasoning that the 400% price hike was justified by costs of materials, packaging and advertising; it seemed clear that the price hike was indeed meant purely to satisfy the company's responsibility to corporate shareholders. The utility of ritonavir is not in question. Dr. Follansbee observed that many in the audience were present at the 1996 CROI discussion of the randomized study of ritonavir 600 mg BID in individuals with less than 50 CD4+ cells; the remarkable outcomes in survival changed our thinking about potential treatment benefits. Abbott has done, and continues to do, important work in HIV treatment, but their exorbitant price increase demands a response from those who provide care for persons with HIV. Dr. Follansbee urged everyone present to read the resolution drafted by the Board and to consider how he or she would like to address this important issue on an individual level. He noted that Abbott had been asked to withdraw financial support for this meeting, and that the International AIDS Society was also refusing funds, unrestricted or otherwise, from the company.

As a brief point of interest, Dr. Follansbee mentioned a poster from CROI, which related to the San Francisco health department's recent announcement regarding the use of azithromycin in syphilis. Poster #771 (p771), from a study conducted in Dublin, Ireland, reviewed a study of rates of syphilis treatment failure among 256 HIV-positive and HIV-negative patients in that city beginning in 2000. Dublin, like San Francisco, is experiencing a syphilis epidemic and health officials are worried about an associated rise in HIV transmission. Using <4-fold decrease in titer within one year as the definition of treatment failure, the study found a failure rate of 39% (31% excluding patients lost to follow-up). Predictive factors did not include sex, age, sexuality, type of treatment (benzathine vs. procaine penicillin), baseline RPR, or HIV status. HIV-positive patients who were not on antiretroviral therapy were more likely to experience syphilis treatment failure. The conclusion from this study is that syphilis treatment algorithms for HIV-positive patients are no less successful than those for HIV-negative patients.

Dr. Follansbee gave his overall impressions of the conference, noting that it was always his favorite of the year, and that this one had been no less interesting than previous ones. Though there was little he could put to immediate use in the clinic, there were many exciting

developments from the virologic standpoint, and in genomics and immunology – indicating new directions in treatment that have not yet been considered. Dr. Follansbee encouraged those present to view the webcast of the keynote lecture delivered by Stephen Lewis, the UN Special Envoy to Africa for HIV/AIDS. The last point of this lecture is that HIV will never be controlled until women gain control of their own bodies and destinies. Dr. Follansbee wondered, in the current context of rhetoric about constitutional amendments and the sanctity of marriage, how successful our own prevention strategies can be when this society is unwilling to acknowledge those who are at risk.

Turning to specific presentations at the conference, Dr. Follansbee reviewed three posters concerning vaccines that were of interest. The first (p722) showed results of a VAMC study comparing rates of pneumococcal vaccine failure among HIV-negative and HIV-positive subjects. Failure in the study was defined as a discharge diagnosis of non-PCP pneumonia or pneumococcal pneumonia, bacteremia, meningitis or sepsis within one year following vaccination. Of the 279 HIV-negative veterans vaccinated, there was one failure (0.36%); among the HIV-positive veterans, 23 out of 604 failed (3.80%). Thus, the pneumococcal vaccine's protective effect is diminished among HIV-positive subjects in comparison with their HIV-negative counterparts. This appeared to hold true as well within various subgroups of subjects with increased susceptibility to pneumococcal disease: African Americans, smokers, binge drinkers, and patients with diabetes and COPD. Dr. Follansbee encouraged providers to

do whatever possible to reduce risk within these groups.

A non-randomized Japanese study (p231) compared the incidence of influenza among HIV-positive patients who had been vaccinated versus those who had chosen not to receive the vaccine. Infection was diagnosed by culture, serology and PCR. Among 328 HIV-positive patients, 9.5% of those vaccinated became infected, compared to 25.8% of non-vaccinated subjects. In patients with CD4+ cell counts <150/mL, there was no difference between the two groups; however, the study confirmed that vaccination does have an impact in the incidence of disease among individuals with higher CD4+ cell counts.

Finally, there was a study (p830) of immune response to hepatitis A vaccination in HIV-positive patients. Of 103 patients that completed the vaccination series, 51 had positive post-vaccine HAV antibody results. Multivariate analysis showed that female sex and higher CD4 count at vaccine were independent predictors of response to vaccine.

Dr. Follansbee concluded the first part of his remarks by reviewing the interesting findings about surgical outcomes of HIV-positive patients. A retrospective Kaiser study (p82), looking at a variety of procedures and their complications, was conducted because of a perception among surgeons that HIV-positive patients were more likely to experience complications related to surgery than HIV-negative patients. The study identified Kaiser patients who had one or more of selected surgical procedures between July 1997 and June 2002 and were diagnosed with HIV prior to surgery. These cases were matched to

HIV-negative controls by gender, age, type of procedure, year of surgery, and medical center. Chart review was conducted through one year post-surgery and lab values (CD4+ count, viral load, WBC count, hemoglobin) were collected. Of 361 case/control pairs identified, 295 were available for analysis. Using various measures (number known alive at 12 months, number experiencing complication and multiple complications, number of revision surgeries, length of hospital stay, number of site infections at 12 months, and number of surgical follow-up visits) an exact analysis showed no significant difference between cases and controls. Higher viral load (>10,000 copies/mL) was a predictor of complications; however, there was no such correlation for CD4+ counts <200/mL. The conclusion was that HIV status alone should not be a criterion in surgical consideration, though viral suppression to below 10,000 copies/mL might improve surgical outcomes among HIV-positive patients.

The French-Italian studies FRISCA I and FRISCA II (p740) also examined surgical outcomes, specifically those related to coronary revascularization. The study compared the number of major adverse cardiac events for HIV+ and HIV- patients following either percutaneous coronary intervention (FRISCA I) or coronary artery bypass graft (FRISCA II). There was no difference between the two groups in FRISCA I. There was an increase in events for HIV+ subjects in FRISCA II, the reasons for which were not clear. The studies concluded that revascularization is feasible and safe for HIV+ patients, and that larger prospective studies are needed.

Dr. Havlir: Hepatitis C Co-infection

The next speaker was Dr. Havlir, who reviewed several studies of HIV/HCV co-infection. In preface, she remarked that the conference had been, as usual, an exciting opportunity to learn more about HIV pathogenesis; however, the tone was rather subdued, and, as Dr. Follansbee noted, there was little that one could rush home and put to practical use. There seemed to be less new information on metabolic outcomes than in any year prior. In general, the conference seemed much less focused on clinical trials; the hepatitis session she attended seemed especially to rely on passive data.

There were, however, results presented from the “Big Three” hepatitis C trials: APRICOT (p112), ACTG 5071 (p110) and RIBAVIC (p117LB). The APRICOT study (AIDS PEGASYS® Ribavirin International Co-Infection Trial) randomized 868 HIV/HCV co-infected subjects in 19 countries to 48 weeks of blinded treatment with interferon-2a 3-MIU TIW plus ribavirin 800 mg QD, peginterferon-2a (40 kD) 180 µg weekly (PEGASYS) plus placebo, or PEGASYS 180 µg weekly plus RBV 800 mg QD. Follow-up was conducted through 72 weeks; the primary efficacy endpoint, sustained virologic response (SVR), was defined as undetectable serum HCV RNA at week 72 (24 weeks off treatment). By this measure the PEG + RBV arm achieved by far the best results, with a 40% SVR, compared with IFN + RBV (12%) and PEG alone (20%). Among subjects with HCV genotype 1 there was across all arms a significant drop in virologic response from week 48 to week 72; subjects with genotypes

2 and 3 achieved much better responses overall, and, in the PEG + RBV arm, the response was sustained at week 72. The number of withdrawals from treatment because of adverse events was similar across the arms. In the PEG + RBV arm, 8% of patients experienced treatment-related serious adverse events, compared to 5% in the IFN + RBV arm and 10% in the PEG + placebo arm. Interferon is an immunosuppressive agent, of course, and CD4+ counts dropped substantially in each arm of the study over the treatment period; CD4+ percentage did not change, and it is unknown what clinical significance, if any, is associated with the lower absolute counts. On the other hand, patients receiving pegylated interferon achieved on average reductions in HIV RNA of 0.5-1.0 log₁₀. Finally, to address theoretical concerns that ribavirin might compete with ZDV, d4T and 3TC for phosphorylation, the study design included a nested pharmacokinetic substudy (*n* = 55). The results showed that ribavirin did not affect the NRTI levels.

The next study, ACTG A5071, randomized 133 subjects to either PEG + RBV or IFN + RBV. As in the APRICOT study, the treatment period was 48 weeks and the follow-up 24 weeks. Ribavirin was given on a dose escalation schedule, 600 mg/day to 1000mg/day. Dr. Havlir pointed out that current data suggests that it is best to start at the maximum tolerable dose, 800 mg. The study’s original primary endpoints were week 24 safety and efficacy; the final analysis aims were to compare end-of-treatment and sustained virologic responses for the two treatment arms, to assess predictors of sustained virologic response, and to assess histologic response. At the end of

treatment, 12% of subjects on the IFN arm and 41% of those on the PEG arm had achieved virologic response; subjects with sustained virologic response were 12% and 27%, respectively. Genotype 2 and 3 subjects again did better than those with genotype 1 virus, of which only 6% and 14% achieved sustained virologic response, respectively. The subject’s status at week 12 on treatment was found to be highly predictive of virologic response, especially for non-responders: of the 63 subjects who did not respond at week 12 with either undetectable HCV RNA or a 2 log₁₀ drop, 100% failed to achieve a sustained virologic response. Many of the virologic non-responders underwent sequential biopsies, which showed that in approximately a third of the subjects in each arm there was a histologic response. What this means clinically is not yet known, but it raises questions about whether or not patients should stop therapy after failing to respond virologically at 12 weeks.

RIBAVIC is a third study that compared PEG+ RBV and IFN+RBV in subjects with HIV/HCV co-infection, again with 48 weeks of treatment followed by 24 weeks off treatment. At 72 weeks, 26% of patients on the PEG+RBV had achieved sustained virologic response, compared to 18% in the IFN+RBV arm. Treatment discontinuation in the study was extraordinarily high, at 42%. This was thought to be related to the high rate of ddI + d4T use among subjects.

Dr. Havlir noted that in HCV mono-infection rates of sustained virologic response are much higher – 63% with PEG+RBV. In the co-infection studies discussed, APRICOT’s 40% was the highest rate found, again with PEG+RBV. All three studies support the idea that in treating HCV, as in treating

HIV, combination therapy proves more effective. The studies also show that genotype 1 patients fare significantly worse, no matter the regimen. Where the studies differ is in the rates of response to treatment, which is difficult to explain, not least because of baseline demographic profiles that are not comparable.

Dr. Deeks: NNRTI Metabolism, Triple NRTI Regimens

Steve Deeks spoke next, and he too began with his general impressions of the conference. He was struck, he said, by what seemed to be a clear effort among the conference planners to focus on virology while downplaying immunology and clinical trials. He noted, however, that there was valuable information to be gained from the discussions of pathogenesis that could be applied in the process of individualizing treatment approaches for patients. He was particularly interested in new findings on the “pathogenesis of treatment response,” and he presented some of these as they related to nucleosides and non-nucleoside RT inhibitors.

First, there was a series of presentations made regarding the host factors that are critical to successful NNRTI therapy. We have known for some time that all of the protease inhibitors and NNRTIs are processed in the liver by a variety of cytochrome P450 isoenzymes. More recently it has been shown that drug transporter, e.g., P glycoprotein, and cytochrome isoenzyme levels and activities vary between individuals, which may impact response to HAART. With this background knowledge, ACTG investigators are conducting the 5097s protocol (a substudy of ACTG

5095), which compares ZDV/3TC+EFV with ZDV/3TC/ABC+EFV and looks at, among other things, differences in efavirenz metabolism. PK analysis has shown that there is a strong association between race and clearance of the drug: compared to the white population, African Americans and Hispanics experience a 32% decrease in clearance – and thus have higher levels of EFV circulating in the bloodstream. There is, in turn, some evidence that low clearance is associated with early discontinuation of EFV. Additionally, as part of the parent 5095 study, genetic testing was performed on subjects to look for single nucleotide polymorphisms in the hepatic enzymes and drug transporters known to be involved in EFV metabolism. Results (p133) of genotype comparisons showed that the homozygous TT genotype, which is more common among blacks than whites, is associated with higher EFV concentrations and higher CNS toxicity. This likely also holds true for nevirapine, and may apply to PIs as well.

Among the clinical implications of the findings regarding NNRTI metabolism is the question of how best to handle drug discontinuation in the setting of treatment interruption. Because the half-life of EFV – up to 100 hours - is considerably longer than that of NRTIs, discontinuing an EFV-based regimen may result in NNRTI resistance. Suggested options for discontinuation are therefore (1) to continue the NRTIs for 7 days after stopping the NNRTI, or (2) to switch to a PI for 1-2 weeks before stopping the regimen. Dr. Deeks noted, however, that although cases have been reported of NNRTI resistance emergence in the scenario of treatment interruption, it has generally not been seen in controlled research settings. Echoing one of the conclusions of a Mark Dybul

STI study presented at the 2003 CROI, he suggested that whether or not NNRTI resistance develops likely depends on how well controlled the virus is at the time of discontinuation.

Dr. Deeks next covered the presentations made on triple NRTI regimens. He reminded the audience that at last summer’s IAS meeting results of two studies of once daily ABC+3TC+TNF showed that subjects on this regimen fared poorly. French investigators looked in the context of the Tonus study at reasons for its failure (p52). Of 36 patients in the study who reached week 24, twelve met the virologic failure endpoint, and the study was closed prematurely by the DSMB. The emergence of resistance in the study was associated with the appearance of the M184V and K65R mutations. In another study (p51), 21/22 patients receiving once daily ddI+3TC+TNF discontinued treatment early because of suboptimal response; again, most patients showed the M184V/I mutation and almost half had K65R. It is unlikely that lack of potency accounts for the rapid failure; one would expect either of these combinations to perform at least as well as Trizivir, which is a generally successful regimen. More likely mechanisms are drug interactions (including intracellular) – though a PK substudy of Tonus found that most subjects had adequate plasma Cmin for all drugs, and all had detectable intracellular triphosphate levels for more than one agent – and low genetic barrier to resistance.

The most compelling data accounting for these regimen failures, said Dr. Deeks, has to do with resistance pathways: K65R’s effect on both susceptibility of the drugs and viral fitness. To explain this he pointed to the COL40263 study of

once daily trizivir + tenofovir (p53). A critical aspect of this study is that, while the pharmacology supports once-daily dosing of 3TC, tenofovir and abacavir, this is not the case for ZDV; the low dose of ZDV given once a day would not be expected to have any dramatic effect on treatment outcome. An interim analysis was performed on 88 subjects who had at least 8 weeks of HIV-1 RNA data, 59% of whom had VL >100,000 copies/mL at baseline. Among all subjects, 79% achieved VL <400 and 67% reached VL <50; among those with baseline VL >100,000, these proportions were 74% and 60%, respectively. This is an outcome consistent with what we would expect of a standard regimen – dramatically different from the previously mentioned results, where ZDV was not a part of the regimen. The lack of K65R in subject genotypes and the improved virologic response that resulted from the addition of once daily ZDV suggest that the drug has an important role in modulating resistance.

What does K65R do? It blocks access of NRTIs to the active site, as 184V does. It decreases the ability of the drug to become incorporated into the DNA synthesis, dramatically so in the case of TNF, ddI and ABC; however, it also decreases excision of the drug that does become incorporated, particularly ZDV. Thus, ZDV in the presence of K65R becomes quite potent, as the virus becomes hypersusceptible to the drug. This, Dr. Deeks concluded, could well account for the success of the COL40263 regimen compared to the NRTI regimens without ZDV.

Dr. Follansbee: Genotype vs. Phenotype, 3TC and Rx failure, Lipoatrophy, Bone Density, Anal Cancer

Dr. Follansbee returned to the dais with a discussion of the relative utility of genotype vs. phenotype resistance testing in making clinical decisions about regimen change. He referred to the 049 study of two high-dose lopinavir/ritonavir regimens in highly experienced subjects (p134), which found that both regimens boosted the LPV trough by 60-70%. The LPV inhibitory quotient (C_{trough}/individual protein binding-adjusted IC₅₀ for HIV) was found to be predictive of virologic success, as was baseline HIV RNA. Interestingly, a third predictor was the NRTI genotype, not the phenotype, suggesting that genotyping, which is more conservative, may be more helpful clinically. A second study, VIHRES (p675), directly compared phenotype and genotype in 158 patients who had failed multiple regimens, with treatment guided by the treating clinician in consultation with a virologist and a clinician expert. The study's conclusion was that neither test conferred an advantage over the other. The only predictor of virologic success was adherence >95%. In short, the genotype vs. phenotype question has not been satisfactorily answered.

Dr. Follansbee next discussed the COLATE 3TC study (p549), noting that he tends to keep most patients on this relatively non-toxic drug regardless of virologic sensitivity. The study randomized 131 patients with incomplete viral suppression on a regimen containing 3TC to either continue or discontinue 3TC, looking at log₁₀ reduction in viral load by AUC measurement, and found no difference between the two groups. Dr. Follansbee

said that with these results he could only continue to wonder if retaining 3TC in his patients' regimens was worthwhile.

He moved on to the topic of metabolic complications, stating that the conference had not provided much new information, other than negative findings on rosiglitazone and some nutritional interventions. One point of interest was the post-hoc analysis (p722) of the BMS 096 and 099 studies, looking at predictors for lipoatrophy. The studies were randomized, double-blind trials of d4T 100 mg extended release (XR/PRC) vs. 40 mg b.i.d. immediate release (IR), and the median follow-up time for both groups was around 2 years. Lipoatrophy was defined observationally by the investigator, and it included peripheral fat loss and facial wasting. The analysis identified triglyceride levels <200 mg/dL at baseline (p = 0.030), age <40 years (p = 0.002), and XR/PRC formulation (p = 0.004) as significant predictors for the reduced incidence of any lipoatrophy.

Next discussed were several studies of bone density. One study (p743) looked at fragility fractures in HIV+ patients at 9 large clinics; of 8600 total patients, 49 were identified with fragility fractures following little or no trauma. With a median follow-up of 10 months, there were recurrent fractures in 9 cases, seven of these at new sites. Only 10/49 patients had undergone DEXA scans for assessment of bone density, and 4/10 were osteoporotic by hip and lumbar assessment. In only 19 of 49 cases was there documentation that treatment, e.g., calcium supplementation, was offered. The investigators concluded that HIV providers are undereducated in the area of evaluation and treatment of decreased bone mineral density. An Italian study (p742) also looked at osteopenia and

osteoporosis, specifically to evaluate the effects of alendronate (Fosamax), vitamin D, and calcium supplementation on bone metabolism and bone mineral density in patients with HIV infection. Forty-one patients were randomized to receive calcium and vitamin D either with or without alendronate. Interim 52-week results in this 104-week study showed little difference between the groups, though the investigators' summary suggested that Fosamax afforded significant improvement in lumbar-sacral bone density. Finally, interim analysis of data from the Women's Interagency HIV Study (WIHS) showed decreased bone density in women with HIV infection (p744). The study compared 3 groups: HIV- (n=88), HIV+ not on HAART (n=90), and HIV+ on HAART (n=94); the presence of osteoporosis/osteopenia at any site, determined by DEXA, was 6.4%, 18.9% and 20.4%, respectively. Longer nevirapine use was associated with higher bone density, while longer abacavir use was associated with lower bone density. (Dr. Follansbee reminded listeners that this was based on interim analysis and cautioned against applying this information clinically.) White race, lower body mass index and self-reported postmenopausal status were also independently associated with lower bone density.

Dr. Follansbee touched briefly on the topic of anal cancer. A poster discussion chaired by Joel Palefsky highlighted the importance of digital examination for diagnosis of cancer, starting at age 35. Palefsky advised using CYTO-TEK liquid technology over the traditional swab/slide methodology; he also opined that the proper intervention for carcinoma in

situ is excision rather than irradiation. A second study (p775) showed greater concordance of anal PAPs when done at regular intervals by the same pathologist. Two other studies looked at rates of anorectal cancer. A CDC study (p777) found the risk of anal cancer to be significantly higher in the HIV+ population, and higher risk was associated with male-male sex, age >45, and more advanced HIV disease. The second study (p778), matching data between the AIDS and cancer registries for San Diego County, found that diagnoses of anal cancer had increased in the era of HAART. Dr. Follansbee provided the caveat that both studies included noninvasive high-grade squamous intraepithelial lesions as cancer diagnoses.

Dr. Havlir: New Drugs, Mother-to-Child Transmission

Dr. Havlir returned to discuss the conference's presentations on new antiretroviral therapies. She noted that new drugs were not well featured, despite our pressing need for them – especially for those patients who have been on sequential therapy for years. There was promising information on a new RT inhibitor, Reverset (RVT), and its benefits for just these patients. Preclinical studies have shown activity against wild-type HIV-1 and mutants resistant to 3TC, ZDV and TNF, long intracellular half-life of the triphosphate, and no mitochondrial toxicity or lactic acid increase; if these results are borne out *in vivo*, this could be a very valuable drug to add to the HAART portfolio. A single-dose clinical study showed excellent oral bioavailability and potent anti-HIV activity (0.4 log₁₀ decrease)

after one dose. The RVT-202 study (p137) randomized 30 naive subjects to one of 3 dose levels of RVT monotherapy: 50, 100, or 200 mg or placebo, once daily for 10 days, to determine safety, efficacy, pharmacokinetics and changes in genotype. Mean change in HIV RNA at 10 days for all three doses was around 1.6 log₁₀, and slight increases in CD4+ cell count were noted in all groups (even placebo). There were no serious AEs, no drug- or dose-related clinical or laboratory toxicities, and no drug discontinuations for any reason. The PK analysis showed that, though dose level did not seem to affect viral load reduction, there were significant differences in plasma concentration among the 3 doses; on genotype, at the 200 mg level, the C_{max} exceeded the inhibitory concentrations of a large variety of mutant HIV strains. Given these promising data, we can look forward to results of the nascent international phase 2b study of treatment-experienced subjects.

Another need is for new agents with different mechanisms. Dr. Havlir noted that, though patients and providers were grateful for the availability of T-20, an oral entry inhibitor would be most welcome. Some data were presented at the conference about efforts to meet this need. First, a study of BMS-488043 (p141) described the antiviral activity, safety and tolerability of this novel small molecule HIV-1 “attachment inhibitor.” This drug binds specifically to gp120 and blocks attachment of gp120 to CD4. Activity is co-receptor independent and effective against all HIV-1 strains. In this monotherapy study two groups of 15 patients were randomized to receive 800mg or 1800 mg BMS-488043 or placebo b.i.d. for 8 days with a high fat

meal. Reported data was from the 800 mg group. Seven of the 12 patients who received drug experienced an approximate 1.0 log₁₀ viral load reduction, and mean change in CD4+ cell count was +106/μL. There were no serious adverse events and no discontinuations from the study. This first clinical trial of a new class of therapy marks an important step forward. There is a good bit of tinkering yet to be done with this drug, including finding an optimal dose and testing it for synergy with other entry inhibitors.

Additionally, there were reports on several CCR5 antagonists in development. The first of these (p139) concerned a dose-escalation study of GW873140 in HIV- persons, which found that the drug was well tolerated. The drug's performance was measured by looking at CCR5 "occupancy" (how long the drug is actually on the CCR5 receptor): 12 hours post once or twice daily dosing. The compound will presumably move forward in trials of HIV+ persons. The second agent, SCH D (p140LB), replaces Schering's earlier drug in this class, SCH C, because of its superior activity and bioavailability and its lack of CYP3A interactions. A 14-day study of 10 mg, 25 mg and 50 mg twice daily in 48 HIV+ persons found mean log₁₀ reductions in viral load of -1.08, -1.56, and -1.62, respectively, and good tolerability. A presentation (p538) on the third CCR5 antagonist, UK-427857, focused on one patient with dual CCR5 and CXCR4 virus, CCR5 predominating, who was mistakenly enrolled in a dose-escalation study. This patient experienced no decrease in HIV RNA, but CCR5 variants were suppressed; after therapy cessation there

was a return to CCR5 dominance. This suggests that dual tropic virus can be treated differentially. We should expect further clinical investigation of this phenomenon.

Dr. Havlir then switched to the topic of mother-to-child transmission (MTCT). The evolving story of MTCT strategies in resource-poor settings has received a great deal of media attention, following the first report of treatment response to AR therapy in women who received single dose nevirapine prophylaxis. Despite predictions that this intervention in women in Africa would not succeed, female activists there mobilized and now a program of short-course prophylaxis to prevent MTCT is in place in many parts of the continent. The next step, of course, will be to expand to full HAART, but there are a number of challenges. Much of the media coverage has been focused on the dangers of AR monotherapy, but Dr. Havlir reminded listeners that this perspective should be balanced by recognition of the many cases of MTCT that have been prevented.

One trial that received a good deal of attention was a study, PHPT2, of adding single dose nevirapine to ZDV prophylaxis among pregnant women in Thailand (p40LB). ZDV is affordable and implemented in many resource-limited countries; however, NVP is also efficacious as prophylaxis, and the effect of combining the two drugs seemed worthy of investigation. The study enrolled 1844 women receiving ZDV in their 3rd trimesters and randomized them to receive (1) NVP at birth (mother and infant), (2) NVP at birth (mother only) or (3) placebo. The placebo arm was discontinued after interim analysis showed a clear benefit to adding NVP:

transmission rates were 2%, 2.8% and 6.3%, respectively for the three arms. Dr. Havlir cautioned listeners to remember that these results were in the context of formula feeding.

A complication associated with administering this regimen is the potential for AR resistance development. In another Thai study (p96), HIV+ AR-naive women were given short-course ZDV (from 34-36 weeks gestation through delivery) plus a single intrapartum dose of NVP; infants were given a single dose of NVP plus 4 weeks of ZDV. Of 190 women who took therapy, delivered and had genotypes completed at one month postpartum, 17% showed NVP resistance and 2% showed ZDV resistance. Among 10 infected infants, two had NVP resistance at 2 months. A South African study (p38) was designed specifically to assess genotypic resistance induced by single-dose NVP in the setting of MTCT prevention. The study enrolled 623 women and followed 456 to a median of 7 weeks postpartum; all but 4 had clade C virus. Following single-dose NVP administration, 40% of mothers and infants showed genotypic NVP resistance at 2 months. Dominant mutations were K103N in mothers and Y181C in infants. More than one NVP dose was associated with higher rates of resistance. The clinical significance of these mutations is not known. Thus, returning to the PHPT2 study (p41LB), we find an evaluation of response to 6 months of combination therapy in women following intrapartum NVP/ZDV exposure. The subjects were treated with NVP + 2 NRTIs after delivery; there were different intervals, it should be noted, between the intrapartum NVP dose and initiation of combination

therapy. At 6 months, response to therapy (viral load < 400 copies/mL) was as follows: 68% among women who had received intrapartum NVP and developed resistance mutations, 80% among women with NVP exposure and no resistance, and 85% in women who had not been given NVP and had no mutations. It appears, then, that drug mutations following NVP exposure do affect the efficacy of the NNRTI-based regimen, although, in this study at least, a significant number of individuals with these mutations nonetheless achieve viral suppression. Importantly, women who initiated combination therapy >6 months after single-dose NVP, with or without resistance mutations, responded better to treatment than those who started earlier.

A related trial, the MIRIAD study (p95), looked at rapid HIV testing of women with undocumented HIV serostatus in 6 US cities, with the rationale that those identified as HIV+ could be offered immediate access to AR prophylaxis. Samples were collected from 3660 women and submitted for both rapid (OraQuick) and standard (Elisa/Western Blot) antibody testing. Turn-around time from blood draw to delivery of results was 70 minutes for the rapid test vs. 28 hours for the Elisa/WB. Twenty-nine patients tested positive, by both methods. The rapid test sensitivity was 100% and specificity was 99.9%; positive predictive value was 94%, compared to 74% with Elisa.

Dr. Havlir reviewed the following in summary. MTCT prophylaxis, though remarkably successful, carries the longer-term cost of drug resistance. When creating a short-term optimal MTCT regimen, we need to take into consideration the drug half-lives. We

should also remember that HIV transmission through breast milk remains a major challenge. New safety warnings on administering NVP to women with CD4+ counts >350 complicate management further. And finally, although it is heartening to hear that rapid HIV testing at the time of delivery is feasible, its application in low-prevalence areas needs further evaluation.

Dr. Deeks: Clinical Trials of Interest

The final presentation was Dr. Deeks' review of several clinical trials results. First, he returned to the 049 study mentioned by Dr. Follansbee, of high-dose LPV/r in 33 heavily pretreated patients (p134). The study compared two dose combinations: LPV 667 mg + RTV 167 mg vs. LPV 400 mg + RTV 300 mg, plus 2 or 3 NRTIs selected by the care provider. At 48 weeks, 58% had HIV RNA <400 copies/mL and 48% had reached <50 copies/mL. There was a trend toward better tolerability in the 667/167 mg arm, with lower incidence of drug-related diarrhea, vomiting and grade 3 and 4 triglycerides. The study determined that predictors of a viral load <400 at week 48 were the following: baseline VL, fold change IC50, number of LPV mutations, active NRTIs and LPV inhibitory quotient. The conclusion was that higher doses of LPV/r may provide LPV concentrations sufficient to overcome certain degrees of LPV resistance, resulting in a significant treatment effect.

Dr. Deeks next discussed the interesting concept of lowering drug pressure to maintain multi-drug resistance, which was examined in the Vista ANRS 109 trial (p649). One dilemma in the treatment of MDR patients is that, while

maintaining a failing full-dose HAART regimen usually results in significant drug toxicity and in continued development of resistance, the interruption of that regimen allows the reemergence of wild type virus with full replicative and pathogenic capacity. As we know, the presence of resistance mutations often weakens the virus; therefore, patients would be well served if we could successfully reduce their drug burden to the minimal amount required to retain those mutations. This French pilot study looked at low-dose IDV/RTV (200/100 mg) + 3TC 150 mg twice daily in patients with MDR HIV (<2 remaining active drugs by genotype). Primary end-points were >25% decrease in CD4 counts (immunologic failure), or >0.7 log increase in plasma HIV RNA (virologic failure) at 2 consecutive monthly visits during the 24-week study. Of 26 patients, 10 (38%) reached a primary endpoint: 6 met immunologic failure, 3 virologic failure, and 1 both. The median increase in viral load at week 24 was 0.22 log₁₀; median slope in CD4+ cell count decreased slightly but did not significantly change. There were no significant changes in the numbers of either protease or RT resistance mutations. It appears, then, that low PI and RTI drug pressure can successfully stabilize HIV evolution and pathogenicity in MDR patients with limited treatment options.

Dr. Deeks next described the FORTE trial (p564), which investigated the strategy of induction on 4 AR drugs followed by a 3-drug regimen. The study randomized 122 treatment-naive patients to either induction/maintenance (PI + NNRTI + 2 NRTIs for 24-32 weeks until viral load reached <50 copies/mL, then NNRTI + 2 NRTIs) or standard therapy (NNRTI + 2 NRTIs). The

primary endpoint was time to virologic failure, defined as viral load >50 copies/mL at 24 and 32 weeks or subsequent rebound >400. At both 24 and 32 weeks, more patients on the standard therapy arm had reached virologic failure. At week 48, mean viral load decrease was 0.86 log₁₀ copies/mL greater in the induction/maintenance arm; 81% of induction/maintenance patients had VL <50, vs. 65% of standard therapy patients; 100% and 86%, respectively, reached VL <400. There was not a significant difference in T-cell increase or in adverse events between groups. The improved virologic results associated with the induction/maintenance strategy are provocative and warrant further research.

Next discussed were the results of BMS A1424-045 (p547), a comparison of lopinavir/ritonavir vs. atazanavir/ritonavir vs. atazanavir/saquinavir. This ongoing study enrolled patients who had failed 2 or more HAART regimens containing at least 1 PI, NNRTI and NRTI, and randomized them (1:1:1) to ATV/r 300/100 mg daily, ATV/SQV 400/1200 mg daily, or LPV/r 400/100 mg twice daily, each combined with tenofovir 300 mg daily and 1 NRTI. Parameters assessed include HIV RNA, CD4 cell count, and safety (including lipids). ATV/r and LPV/r were similarly effective, though discontinuation prior to week 48 for treatment failure or lack of efficacy occurred in 5% of LPV/r patients vs. 14% of those on ATV/r. ATV, with RTV or SQV, demonstrated a markedly better lipid profile than LPV/r.

Dr. Deeks concluded with coverage of ACTG 372A, the abacavir intensification study. The rationale for the study was that strengthening an already successful regimen should maximize viral suppression and improve the durability of the regimen. In this trial, 229 ZDV-experienced subjects on therapy with IDV + ZDV (or d4T) + 3TC with HIV RNA <500 copies/mL were randomized to add ABC 300 mg twice daily or placebo. The composite endpoint was confirmed virologic failure (2 consecutive HIV RNAs >200 copies/mL) and treatment discontinuation. Results were that, by a number of measures (ultrasensitive viral load, proviral DNA, frequency of VL “blips,” emergence of mutations, CD4+ cell counts, mortality and tolerability) there was no difference between the abacavir and placebo arms. As the study authors noted, the ABC intensification strategy “cannot be recommended without additional clinical trial data.”

The Community Consortium is grateful for the generous support from Agouron, Boehringer Ingelheim, Bristol-Meyers Squibb, BTG, Gilead, GlaxoSmithKline, Merck & Co., Ortho Biotech, Roche, and Virologic Inc., who made this program 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 82 of the 1818 study participants.

We established a new relationship with clinician/investigators at UCSF Fresno and are delighted to report that Simon Paul, M.D., and Jill Langford, R.N., have already randomized their first 4 participants. Congratulations! We also welcome Toby Dyner, M.D., as our latest SMART subsite! Dr. Goldyn and Dr. Pope have decided to close their private practice office. We wish them the best in their future endeavors.

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 substudy has 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 almost 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 out 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 initial results of the Multi-Drug Resistant (MDR) study were published in the August 28, 2003 *New England Journal of Medicine*, with Dr. Jody Lawrence as the lead author. The study will be closing to followup as of June 30, 2004 and final close-out visits will be performed by the end of August. The study has definitely set the mark for current views on managing drug resistance with STI's and the further need for evaluation of STI's 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)

Do you have patients who have chosen to remain antiviral naïve or who have been long-term non-progressors? The CPCRA Long Term Monitoring team is looking to enrich follow-up of such patients in the LTM database. If you have individuals who may be interested to contributing to the general knowledgebase regarding naïve and LTNP patients and you are currently a collaborating Consortium clinician/investigator, please let your clinical research nurse know. Such individuals are often eager to participate in observational studies so that their experience can be counted! To date, 3,180 patients are being followed on LTM nationwide, including 153 from our site.

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, 22 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.cmcr.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

Total Enrollments

927

Stay tuned for future analyses from this incredible local registry!

Future Studies

Oyster Mushrooms

The Community Consortium will soon begin 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 ≥ 190 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 has successfully competed for funding from the Center for Medicinal Cannabis Research (CMCR) to perform another marijuana study. This study, which will enroll 20 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. Stay tuned for more details regarding this exciting study.

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.

episodic treatment with open label acyclovir. The ACE study, conducted by co-PI's Dr. Konathan Fuchs and Dr. Susan Buchbinder, will be enrolling 315 HIV-negative gay or bisexual men who are infected with HSV-2. For information on this study contact the study hotline at: 415-437-HSV2 or go to the website at: www.sfajidsresearch.org

The ACE Study

The San Francisco Department of Public Health's HIV Research Section is conducting a study designed to assess whether suppression of genital herpes with acyclovir will help prevent the acquisition of HIV. Mounting evidence has shown that even sub-clinical genital herpes infection can double a person's risk of becoming HIV infected, and that antiviral therapy can prevent HSV-2 transmission in serodiscordant couples.

Participants will be assigned at random to either 400mg twice daily of placebo or acyclovir and will receive risk reduction counseling during one-year of followup. Any participant with symptomatic outbreaks will be provided