

Annotated List of CPCRA Articles

Note: The articles in this list have been published or are in press.

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CPCRA Protocol-Specific Articles

CPCRA 001-TOXO

A Randomized Prospective Study of Pyrimethamine Therapy for Prevention of Toxoplasmic Encephalitis in HIV-Infected Individuals with Serologic Evidence of Latent *Toxoplasma Gondii* Infection

Jacobson MA, Besch CL, Child C, Hafner R, Matts JP, Muth K, et al. Primary prophylaxis with pyrimethamine for toxoplasmic encephalitis in patients with advanced HIV disease: Results of a randomized trial. *J Infect Dis* 1994;169:384-394.

In a placebo-controlled study of clindamycin and pyrimethamine for prophylaxis of toxoplasmic encephalitis (TE), researchers found a significantly higher death rate among patients receiving pyrimethamine. There was insufficient power to compare the treatment arms with respect to prevention of TE because the event rate was too low; however, in observational analyses within each treatment group there was a difference in the event rate between patients receiving aerosolized pentamidine or trimethoprim-sulfamethoxazole for PCP prophylaxis. An additional TE prophylaxis may be unnecessary for patients receiving trimethoprim-sulfamethoxazole. Further research is necessary to define the dose and frequency of trimethoprim-sulfamethoxazole in preventing PCP and to identify the best TE prophylaxis regimen for patients who are TMS- intolerant.

Jacobson MA, Besch CL, Child C, Hafner R, Matts JP, Muth K, et al. Toxicity of clindamycin as prophylaxis for AIDS-associated toxoplasmic encephalitis. *Lancet* 1992;339(8789):333-334.

In a placebo-controlled study of clindamycin and pyrimethamine for prophylaxis of toxoplasmic encephalitis (TE), researchers found that patients treated with clindamycin were more likely to experience an adverse effect that necessitated withdrawal of the study drug than those who received placebo. Therefore, the clindamycin arm was terminated prematurely, although the study continued in order to evaluate the efficacy of pyrimethamine for TE prophylaxis. The findings of this trial suggested that clindamycin, which has been identified as a candidate for TE prophylaxis, would be poorly tolerated as TE prophylaxis.

Jacobson MA, Besch CL, Child C, Hafner R, Muth K, Deyton L. Community Programs for Clinical Research on AIDS: Description of a randomized prospective study of clindamycin versus pyrimethamine for prevention of *toxoplasma gondii* infection. *Eur J Clin Microbiol Infect Dis* 1991;10(3):195-198.

The CPCRA initiated a randomized, placebo-controlled study of clindamycin and pyrimethamine for prophylaxis of toxoplasmic encephalitis in patients who are coinfecting with *toxoplasma gondii* and HIV. The study was designed to determine whether antimicrobial prophylaxis was superior to careful monitoring of at-risk patients and to evaluate the safety and efficacy of the two best candidate agents for preventing toxoplasmic encephalitis.

CPCRA 002-DDI/DDC

A Prospective, Randomized, Open-Label, Comparative Trial of Dideoxyinosine (ddI) Versus Dideoxycytidine (ddC) in HIV-Infected Patients Who Are Intolerant of or Who Have Failed Zidovudine (ZDV) Therapy

Goldman AI, Carlin BP, Crane LR, Launer C, Korvick JA, Deyton L, et al. Response of CD4 lymphocytes and clinical consequences of treatment using ddI or ddC in patients with advanced HIV infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996;11(2):161-169.

The value of CD4+ lymphocyte counts as a surrogate marker in persons with advanced HIV-infection during antiretroviral treatment was assessed using longitudinal models and data from the CPCRA ddI/ddC trial of HIV-infected patients. A CD4 + cell count response was not a good surrogate marker in this study.

CPCRA 002-DDI/DDC, cont.

Fleming TR, Neaton JD, Goldman A, DeMets DL, Launer C, Korvick J, et al. Insights from monitoring the CPCRA didanosine/zalcitabine trial. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;10(Suppl.2):S9-S18.

The design, conduct, and analysis of clinical trials that evaluate the safety and efficacy of treatment interventions in patients with HIV infection provide many scientific challenges. The results of this study provided important insights into how a data safety monitoring board can reduce the risk of inappropriate early study termination. The trial also provided valuable insights into how treatment effects should be assessed, revealing inconsistencies between effects on the CD4 surrogate end point and effects on primary clinical efficacy end points and showing the incompleteness of the standardly employed definition of AIDS progression. Finally, the results of this ddI/ddC trial are used to examine the role of covariate adjustment.

Abrams DI, Goldman AI, Launer C, Korvick JA, Neaton JD, Crane LR, et al. A comparative trial of didanosine or zalcitabine after treatment with zidovudine in patients with human immunodeficiency virus infection. *N Engl J Med* 1994;330(10):657-662.

The CPCRA multicenter, open-label trial compared didanosine and zalcitabine monotherapy in HIV-infected patients with CD4+ cell counts ≤ 300 mm³ or AIDS who could not tolerate zidovudine treatment or who have had disease progression despite it. The study found that zalcitabine was as efficacious as didanosine in delaying disease progression, including death, and suggested to clinicians that zalcitabine can be used as an alternative second-line therapy. The toxicity profiles of didanosine and zalcitabine should be an important consideration in choosing the appropriate antiretroviral therapy for individual patients.

CPCRA 003-ODB

The Observational Data Base Project: A Community-Based Longitudinal Study of HIV-Infected Individuals

Torres RA, Neaton J, Wentworth D, Barr MR, Abrams D, Sherer R, et al. Acyclovir use and survival among human immunodeficiency virus-infected patients with CD4 cell counts of $< 500/\text{mm}^3$. *Clin Infect Dis* 1998;26:85-90.

The study analyzes the effects of acyclovir use on survival and disease progression in a large cohort of HIV-infected persons enrolled in an observational study. This is the largest reported observational multicenter cohort of HIV-infected patients followed prospectively over time, where the effect of acyclovir use on mortality has been analyzed. Overall, 31% of the patients enrolled in cohort reported taking acyclovir at some time during followup, and 15% reported taking the drug at baseline. Increased mortality rates were associated with acyclovir use, irrespective of previous history of herpes simplex or zoster, or previous AIDS diagnosis. If acyclovir use does confer a survival benefit to HIV-positive persons, that benefit is likely to be small and will only be reliably detected through a well-planned, adequately powered, randomized and controlled prospective clinical trial with long-term follow-up and retention of study participants.

Burns DN, Hillman D, Neaton JD, Sherer R, Mitchell T, Capps L, et al. Cigarette smoking, bacterial pneumonia and other clinical outcomes in HIV-1 Infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996;13(4):374-383.

Cigarette smoking has been associated with impaired immune defenses and an increased risk of certain infectious and neoplastic diseases in HIV-1 seronegative populations. Differences in clinical outcomes between never, former, and current cigarette smokers were assessed using proportional hazard regression analysis. After adjustment for CD4+ cell count, prior disease progression, use of antiretroviral therapy, and other covariates, there was no difference between current smokers and never smokers in the overall risk of opportunistic diseases or death. However, current smokers were more likely to develop bacterial pneumonia, oral candidiasis, and AIDS dementia complex. In addition, current smokers were less likely to develop Kaposi's sarcoma and several other non-respiratory tract diseases. If confirmed by other studies, these findings have important clinical implications.

CPCRA 004/ACTG 177-TB/PPD+

Prophylaxis Against Tuberculosis (TB) in Patients with Human Immunodeficiency Virus (HIV) Infection and Confirmed Latent Tuberculosis Infection

Gordin FM, Cohn D, Matts JP, Chaisson RE, O'Brien RJ. Hepatotoxicity of rifampin and pyrazinamide in the treatment of latent tuberculosis infection in HIV-infected persons: Is it different than in HIV negative persons? *Clin Infect Dis* August 15, 2004;39(4):561-565.

Background. In 2000, results of a multinational trial demonstrated that a 2-month course of rifampin and pyrazinamide (RZ) was as effective as isoniazid (INH) in reducing tuberculosis in human immunodeficiency virus (HIV)-infected individuals with latent tuberculosis infection (LTBI). After the release of new guidelines, the Centers for Disease Control and Prevention received reports of severe hepatotoxicity associated with the use of the RZ regimen for the treatment of LTBI in the general population. To better understand the occurrence of hepatotoxicity in an HIV-infected population, we conducted a more detailed analysis of the liver function test results obtained in the multinational trial of RZ. **Methods.** At study entry, patients were required to have a bilirubin level of ≤ 2.5 mg/dL and both an aspartate aminotransferase (AST) level and an alkaline phosphatase level of ≤ 5 times the upper limit of normal. Patients with acute hepatitis were excluded. At months 1 and 2 of the study, all patients had bilirubin and AST levels measured. **Results.** There was no difference between the RZ and INH groups with regard to AST level or bilirubin level at baseline. An increase in the AST level of ≥ 40 U/L was associated with the use of INH and older age; and an increase in the bilirubin level of ≥ 0.5 mg/dL was associated with the use of RZ, male sex, and nonwhite race ($P < .05$). An absolute AST level of >250 U/L occurred in 12 of 745 INH recipients and in 15 of 721 RZ recipients ($P = .56$), and an absolute bilirubin level of >2.5 mg/dL occurred in 5 of 743 INH recipients and 13 of 718 RZ recipients ($P = .06$). **Conclusions.** These data demonstrate very little liver injury associated with either INH or RZ in the HIV-infected subjects, leaving unclear the reasons for serious RZ-related liver damage in the general population.

Gordin F, Chaisson RE, Matts JP, Miller C, de Lourdes Garcia M, Hafner R, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: An international randomized trial. *JAMA* 2000;283(11):1445-1450.

This paper describes a randomized open-label controlled trial that studied HIV-positive persons with a positive tuberculin skin test in outpatient clinics in the United States, Mexico, Haiti, and Brazil. The study compared a 2-month regimen of daily rifampin-and-pyrazinamide with a 12-month regimen of daily isoniazid in preventing tuberculosis in HIV-infected persons. The primary endpoint was culture proven tuberculosis. Secondary endpoints were proven or probable tuberculosis, adverse events and death. There were no significant differences in rates for confirmed or probable tuberculosis, HIV progression, death, or overall adverse events. Neither regimen appeared to lead to the development of drug-resistant tuberculosis. The study concluded that, for preventing tuberculosis in HIV-infected patients, a regimen of rifampin-and-pyrazinamide, given daily for 2 months, is similar in safety and efficacy to a 12-month regimen of daily isoniazid. This shorter regimen offers practical advantages both to patients and to tuberculosis control programs.

CPCRA 005-TB Anergic

Prophylaxis Against Tuberculosis (TB) in Patients With Human Immunodeficiency Virus (HIV) Infection and Suspected latent Tuberculosis Infection

Gordin FM, Matts JP, Miller C, Brown LS, Hafner R, John SL, et al. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. *N Engl J Med* 1997;337(5):315-20.

This study evaluated the effectiveness of providing isoniazid prophylaxis to anergic, HIV-infected persons with risk factors for tuberculosis. Due to the low incidence of tuberculosis in our study, we observed no significant benefit associated with isoniazid use. This cohort was highly representative of groups perceived to be at risk for tuberculosis in the United States and, without a more accurate method to detect latent tuberculosis, it would not be possible to identify individuals who are likely to benefit from prophylaxis. The results of this study, therefore, do not support the use of isoniazid preventive therapy for HIV-infected, anergic individuals in the United States as had been suggested by the CDC other than in specific high-risk situations, such as individuals who are recent close contacts of active cases of tuberculosis.

CPCRA 006-PCP-TMS

A Randomized, Comparative, Prospective Study of Daily Trimethoprim/Sulfamethoxazole (TMS) and Thrice-Weekly TMS for Prophylaxis Against PCP in HIV-Infected Patients

El-Sadr WM, Luskin-Hawk R, Yurik TM, Walker J, Abrams D, John SL, et al. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of *Pneumocystis carinii* pneumonia in Human Immunodeficiency Virus-infected persons. *Clin Infect Dis* 1999;29:775-783.

We enrolled 2,625 human immunodeficiency virus-infected patients into a randomized trial to assess the efficacy and tolerability of daily vs. thrice-weekly trimethoprim-sulfamethoxazole for prophylaxis of *Pneumocystis carinii* pneumonia (PCP). Overall estimates for efficacy end points favored daily trimethoprim-sulfamethoxazole, although rates of intolerance were higher among patients receiving that dose. Daily trimethoprim-sulfamethoxazole may offer advantages as a first choice for PCP prophylaxis; thrice-weekly dosing is an appropriate option for patients intolerant of the daily dose.

CPCRA 007-NuCombo

A Randomized, Comparative Trial of ZDV Versus ZDV Plus ddI Versus ZDV Plus ddC in HIV-Infected Patients

Saravolatz LD, Winslow DL, Collins G, Hodges JS, Pettinelli C, Stein DS, et al. Zidovudine alone or in combination with didanosine or zalcitabine in HIV-infected patients with the acquired immune deficiency syndrome or fewer than 200 CD4 cells per cubic millimeter. *N Engl J Med* 1996;335(15):1099-1106.

In patients with advanced HIV infection, combination therapy with zidovudine and either didanosine or zalcitabine was studied and found not to be superior to zidovudine therapy alone. However, these combinations may be more effective than zidovudine monotherapy in patients with little or no previous zidovudine treatment.

CPCRA 008-TB Booster

Two-Stage Tuberculin (PPD) Skin Testing in Individuals with Human Immunodeficiency Virus (HIV) Infection

Webster CT, Gordin FM, Matts JP, Korvick JA, Miller C, Muth K, et al. Two-stage tuberculin skin testing in individuals with human immunodeficiency virus infection. *Am J Respir Crit Care Med* 1995;151: 805-808.

The investigators in this CPCRA study estimated the occurrence of the booster effect in a population infected with the human immunodeficiency virus (HIV) and assessed the relationship between the booster effect, T-lymphocyte CD4+ cell counts, tuberculosis (Tb) risk categories, and HIV exposure categories. The major conclusions and impact on clinical practice showed the following: 1) the booster effect occurs in a small percentage (2.7%) of HIV-infected patients; 2) age, race, CD4 cell count, IDU, anergy status, Tb risk factors, and HIV exposure categories were NOT predictive of boosting; and 3) the two-stage procedure is probably of limited value in the diagnosis of latent tuberculosis infection in HIV-infected persons.

CPCRA 009/ACTG 196-MAC Prophylaxis

A Prospective, Randomized, Comparative Study of the Safety and Efficacy of Clarithromycin versus Rifabutin versus the Combination of Clarithromycin Plus Rifabutin for the Prevention of MAC Bacteremia or Disseminated MAC Disease in HIV-infected Patients With CD4 <100 Cells/mm³

Benson CA, Williams PL, Cohn DL, Becker S, Hojczyk P, Nevin T, et al. Clarithromycin or rifabutin alone or the combination for primary prophylaxis of *Mycobacterium avium* complex disease in patients with AIDS. A randomized, double-blind, placebo-controlled trial. *J Infect Dis* 2000;181:1289-97.

The efficacy and safety of clarithromycin, rifabutin, and the combination for prevention of *Mycobacterium avium* complex (MAC) disease were compared in a randomized, double-blinded, placebo-controlled trial in 1178 patients with AIDS and ≤ 100 CD4+ T cells/ μ L. Clarithromycin reduced the risk of MAC disease by 44% and the combination by 57% compared with rifabutin. The combination was not more effective than clarithromycin. There were no differences in survival in the three arms. From patients who failed prophylaxis with clarithromycin or the combination, 29% and 27% of MAC isolates, were resistant to clarithromycin, respectively. Dose-limiting adverse effects occurred in 16% of those on clarithromycin, 18% on rifabutin, and 31% on the combination. This study supports the recommendation for use of clarithromycin as a first-line agent for the prevention of MAC disease in patients with HIV infection and advanced immunosuppression, but not the use of combination therapy for prophylaxis.

CPCRA 010-Women's Fungal

A Randomized Prospective, Double-Blind Study Comparing Fluconazole with Placebo for Primary and Secondary Prophylaxis of Mucosal Candidiasis in HIV-Infected Women

Vazquez JA, Peng G, Sobel JD, Steele-Moore L, Schuman P, Holloway W, Neaton JD. Evolution of antifungal susceptibility among *Candida* species isolates recovered from Human Immunodeficiency Virus-infected women receiving fluconazole prophylaxis. *Clin Infect Dis* 2001; 33:1069-1075.

The effect of fluconazole on the susceptibility of *Candida* isolates recovered from women infected with human immunodeficiency virus (HIV) was evaluated in a randomized, double-blind, placebo-controlled trial. Women with CD4+ cell counts of ≤ 300 cells/mm³ received either fluconazole (200 mg/week) or placebo as prophylaxis. The antifungal susceptibility of specimens was evaluated. One patient who received fluconazole and 2 patients assigned to placebo had *Candida Albicans* isolates recovered that were resistant to fluconazole (MIC, ≥ 64 μ g/mL). Eleven patients assigned fluconazole and 4 patients assigned placebo has non-*albicans Candida* strains (all *Candida glabrata*) recovered that were resistant to fluconazole. There was significant azole cross-resistance among the non-*albicans Candida* species isolates. Although the rate of azole resistance did not significantly increase after fluconazole prophylaxis, there was a trend toward more in vitro azole resistance in *C. glabrata* isolates from patients assigned fluconazole. Moreover, the majority of resistant vaginal isolates of *Candida* species were recovered after initiation of open-label fluconazole use.

Vazquez JA, Sobel JD, Peng G, Steele-Moore L, Schuman P, Holloway W, et al. Evolution of vaginal *Candida* species recovered from Human Immunodeficiency Virus-infected women receiving fluconazole prophylaxis: The emergence of *Candida glabrata*? *Clin Infect Dis* 1999;28:1025-31.

The effect of fluconazole prophylaxis on the vaginal flora of 323 HIV-infected women was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial. The effect of fluconazole prophylaxis can be attributed to the reduction in vaginal *C. albicans* colonization; however, *C. glabrata* colonization rapidly supervened.

Capps, L.; Peng, G.; Doyle; El-Sadr, W.; Neaton, JD. Sexually transmitted infections in women infected with the human immunodeficiency virus. *Sex Transm Dis* 1998;25(8):443-447.

Twenty-five percent of 323 HIV-infected women developed new STIs while participating in a trial. Prevention efforts should be emphasized among high-risk HIV-infected patients.

CPCRA 010-Women's Fungal, cont.

Schuman P, Capps L, Peng G, Vazquez J, El-Sadr W, Goldman AI, et al. Weekly fluconazole for the prevention of mucosal candidiasis in women with HIV infection. A randomized, double-blind, placebo controlled trial. *Ann Intern Med* 1997;126(9):689-696.

In patients with HIV infection, mucosal candidiasis is a frequent complication. Weekly fluconazole (200 mg) appears safe and effective in preventing oropharyngeal and vaginal candidiasis. This regimen has a useful role in the management of HIV-infected women at risk for recurrent mucosal candidiasis.

CPCRA 017-TB Registry

A Registry of Tuberculosis Cases in the CPCRA

Gordin FM, Nelson ET, Matts JP, Cohn DL, Ernst J, Benator D, et al. The impact of human immunodeficiency virus on drug-resistant tuberculosis. *Am J Respir Crit Care Med* 1996;154(5):1478-1483.

In order to examine the relationship of HIV infection to drug-resistant tuberculosis in other selected regions of the United States, a registry of cases of culture-proven tuberculosis was established. Results of this study showed that HIV infection is associated with increased rates of resistance to antituberculosis drugs in the New York City area. In areas outside of New York City, HIV-infected U.S.-born persons have higher rates of drug resistant tuberculosis than non-HIV infected U.S.-born persons. MDR tuberculosis is occurring predominantly in the New York City area and is highly correlated with HIV infection.

CPCRA 018-TB/HCWs

PPD Conversion Rates Among Health Care Providers Who Work with HIV Infected Populations

Zahnow K, Matts JP, Hillman D, Finley E, Brown Jr LS, Torres RA, et al. Rates of tuberculosis infection in healthcare workers providing services to HIV-infected populations. *Infect Control Hosp Epidemiol* 1998;19:829-835.

The objective of the study was to determine the relationship of demographic and occupational factors to tuberculosis infection rates in health care workers (HCWs) providing services to HIV-infected individuals. Neither the percentage of patients seen who were HIV-infected, nor the amount of contact with HIV-infected patients was related to the rate of tuberculosis infection. These data provide some reassurance that caring for HIV-infected patients is not in and of itself related to an increased prevalence of tuberculosis infection among HCWs. The risk of tuberculosis infection appears to be related to the prevalence of the disease in the individual community.

CPCRA 019/ACTG 222-TB Treatment

The Treatment of Pulmonary Mycobacterium Tuberculosis in HIV Infection

El-Sadr WM, Perlman DC, Matts JP, Nelson ET, Cohn DL, Salomon N, et al. Evaluation of an intensive intermittent-induction regimen and duration of short-course treatment for human immunodeficiency virus-related pulmonary tuberculosis. *Clin Infect Dis* 1998;26:1148-1158.

The rise of tuberculosis (TB), including drug-resistant TB, among HIV-infected patients underscores the importance of identifying new agents and regimens that improve treatment outcomes. This study examined the response to a largely intermittent four-drug regimen (isoniazid, rifampin, pyrazinamide, ethambutol) and whether adding a quinolone, levofloxacin, would improve 8-week culture response to therapy in HIV-related pulmonary TB. The study results provide strong evidence that a four-drug largely intermittent induction regimen is highly efficacious in the initial treatment of HIV-related pulmonary TB. Both regimens were comparably well tolerated. There was no added benefit noted with the addition of levofloxacin in this population.

CPCRA 019/ACTG 222-TB Treatment, cont.

Perlman DC, El-Sadr WM, Nelson ET, Matts JP, Telzak EE, Salomon N, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. *Clin Infect Dis* 1997;25:242-246.

This paper evaluates the effect of HIV disease stage on chest radiograph (CXR) findings among patients with HIV-related pulmonary tuberculosis. The study demonstrates associations of certain CXR findings with HIV disease stage. Knowledge of immunosuppression level is important when evaluating CXR in HIV-infected patients which may reflect variations in pathophysiology at different degrees of immunosuppression.

Perlman DC, El-Sadr WM, Heifets LB, Nelson ET, Matts JP, Chirgwin K, et al. Susceptibility to levofloxacin of *Mycobacterium tuberculosis* isolates from patients with HIV-related tuberculosis and characterization of a strain with levofloxacin monoresistance. *AIDS* 1997;11:1473-1478.

This paper reports on the susceptibility to levofloxacin on *Mycobacterium tuberculosis* isolates from patients with HIV related TB. One isolate, obtained from a patient who had been treated with levofloxacin for chronic bronchiectasis, was resistant with an MIC = 16 µg/mL and was demonstrated to have a unique point mutation in *gyrA*. 134/135 isolates (99%) were susceptible with an MIC ≤ 1.0 µg/mL. Clinical TB isolates were generally susceptible to levofloxacin. However, the occurrence of resistance highlights the need for circumspection in the use of fluoroquinolones in the setting of potential TB and for monitoring of fluoroquinolone resistance rates.

CPCRA 022-Acupuncture

The Efficacy of a Standardized Acupuncture Regimen and Amitriptyline Compared With Placebo as a Treatment for Pain Caused by Peripheral Neuropathy in HIV-infected Patients

Shlay JC, Chaloner K, Max MB, Flaws B, Reichelderfer P, Wentworth D, et al. Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: A randomized controlled trial. *JAMA* 1998;280:1590-1595.

In a randomized, placebo-controlled trial with patients enrolling into one of three options: a standardized acupuncture regimen (SAR) versus control points (CP), amitriptyline (75 mg) versus placebo, or both using 2x2 factorial design, patients received treatment for 14 weeks and rated their pain daily in a diary. Of 250 patients enrolled, 239 were in the acupuncture comparison and 136 were in the amitriptyline comparison. For both the acupuncture and amitriptyline comparison, change in pain score was not significantly different between the two groups. This is the largest reported randomized, placebo-controlled clinical trial of symptomatic treatment of HIV-related peripheral neuropathy. Neither this SAR nor amitriptyline was effective in relieving pain. Additional clinical trials in HIV-associated neuropathies are needed.

CPCRA 023-CMV

A Randomized, Comparative, Placebo-Controlled Trial of the Safety & Efficacy of Oral Ganciclovir for Prophylaxis of Cytomegalovirus (CMV) Retinal and Gastrointestinal Mucosal Disease in HIV-Infected Individuals with Severe Immunosuppression

Brosgart CL, Louis TA, Hillman DW, Craig CP, Alston B, Fisher E, et al. A randomized, placebo controlled trial of the safety and efficacy of oral ganciclovir for prophylaxis of cytomegalovirus disease in HIV-infected individuals. *AIDS* 1998;12(3):269-277.

The safety and efficacy of oral ganciclovir for preventing CMV disease in persons with severe immunosuppression were evaluated. The major findings were as follows: 1) oral ganciclovir did not prevent CMV retinal or gastrointestinal mucosal disease; 2) oral ganciclovir did not prevent death; 3) oral ganciclovir did not prevent CMV disease or death; 4) oral ganciclovir was significantly associated with more reportable adverse experiences; 5) oral ganciclovir was significantly associated with more grade 3 or higher neutropenia events; and 6) a subgroup analysis suggested a possible ddI-oral ganciclovir interaction that requires further research.

CPCRA 026/ACTG 238-MDRTB

A Prospective Study of Multidrug Resistance and a Pilot Study of the Safety and Clinical and Microbiologic Response to Levofloxacin in Combination With Other Antimycobacterial Drugs for Treatment of Multidrug-Resistant Pulmonary Tuberculosis in HIV-Infected Patients

Telzak EE, Chirgwin KD, Nelson ET, Matts JP, Sepkowitz KA, Benson CA, et al. Predictors for multidrug-resistant tuberculosis among HIV-infected patients and response to specific drug regimens. *Int J Tuberc Lung Dis* 1999;3(4):337-43.

Mortality associated with HIV-related multidrug-resistant tuberculosis (MDRTB) is reduced with effective early therapy. Identifying predictors of, and effective regimens for, MDRTB is critical. Patients were prospectively evaluated for MDRTB. The conclusions reached showed that a history of treatment for tuberculosis was the only predictor for MDRTB among a cohort of HIV-infected patients with tuberculosis. In addition, this prospective study supports the results of prior retrospective studies that effective treatment impacts on mortality. Current second-line treatment, including high dose levofloxacin, appears to be well tolerated.

CPCRA 027-MAC Treatment

An Open-Label, Randomized, Trial of Four Treatment Regimens for Patients With Disseminated *Mycobacterium Avium* Complex Disease and Acquired Immunodeficiency Syndrome (AIDS)

Cohn DL, Fisher EJ, Peng GT, Hodges SJ, Chesnut J, Child CC, et al. A prospective randomized trial of four three-drug regimens in the treatment of disseminated *Mycobacterium avium* complex disease in AIDS patients: Excess mortality associated with high-dose clarithromycin. *Clin Infect Dis* 1999;29:125-33.

The optimal regimen for treatment of *Mycobacterium avium* complex (MAC) disease has not been established. Eighty-five AIDS patients with disseminated MAC disease were randomized to receive a three-drug regimen of clarithromycin, rifabutin or clofazimine, and ethambutol. Two dosages of clarithromycin were compared. The Data and Safety Monitoring Board recommended discontinuation of the clarithromycin dosage comparison and continuation of the rifabutin vs. clofazimine comparison. Bacteriologic outcomes were similar among treatment groups. In treating MAC disease in AIDS patients, the maximum dose of clarithromycin should be 500 mg. b.i.d.

CPCRA 030-Fluconazole/Methadone-pk

A Study to Assess the Effect of Concomitant Administration of Fluconazole on the Clinical Pharmacokinetics of Methadone

Cobb MN, Desai J, Brown Jr LS, Zannikos PN, Rainey PM. The effect of fluconazole on the clinical pharmacokinetics of methadone. *Clin Pharmacol Ther* 1998;63:655-62.

This paper describes a study which evaluated the pharmacokinetics of methadone in the presence of fluconazole therapy in patients on methadone maintenance. The study demonstrated that methadone concentrations were increased, although renal clearance was not affected. Despite the exposure to higher methadone, fluconazole-treated patients did not exhibit signs or symptoms of narcotic overdose.

CPCRA 034/ACTG 277-PCP-INT2

A Randomized, Comparative Study of Daily Dapsone and Daily Atovaquone for Prophylaxis Against PCP in HIV-infected Patients Who Are Intolerant of Trimethoprim and/or Sulfonamides

El-Sadr WM, Murphy RL, Yurik TM, Luskin-Hawk R, Cheung TW, Balfour HH, et al. Atovaquone compared with dapsone for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. *N Engl J Med* 1998;339:1889-1895.

This paper describes a multicenter, open-label, randomized trial comparing daily atovaquone with daily dapsone for the prevention of *P. carinii* pneumonia among patients infected with HIV who could not tolerate trimethoprim-sulfamethoxazole. *P. carinii* pneumonia developed in 122 of 536 patients assigned to atovaquone, as compared with 135 of 521 in the dapsone group. The rates of *P. carinii* pneumonia were similar in the two treatment groups. It was concluded that, among patients who cannot tolerate trimethoprim-sulfamethoxazole, atovaquone and dapsone are similarly effective for the prevention of *P. carinii* pneumonia. The results support the continuation of dapsone prophylaxis among patients who are already receiving it; however, among those not receiving dapsone, atovaquone is better tolerated and may be the preferred choice for prophylaxis against *P. carinii* pneumonia.

CPCRA 038-Nutrition

An Open-Label, Randomized, Three-Arm, Comparative Trial of a Caloric Supplement With Peptides and Medium-Chain Triglycerides Versus a Caloric Supplement With Whole Protein and Long-Chain Triglycerides Versus No Caloric Supplement for the Prevention of Weight Loss in Individuals With AIDS Who Take a Daily Multivitamin and Mineral Supplement

Williams SB, Bartsch G, Muurahainen N, Collins G, Raghavan SS, Wheeler D. Protein intake is positively associated with body cell mass in weight-stable HIV-infected men. *J Nutrition* 2003; 133:1143-1146.

Depletion of body cell mass (BCM) in human immunodeficiency virus (HIV)-infected patients is strongly associated with disease progression and death. Although whole-body protein turnover is increased in HIV infection, it is not known whether protein intake is independently associated with BCM. The purpose of this study was to determine the associations, if any, between protein intake and several body composition variables in 467 weight-stable, HIV-infected men with CD4 <200 cells/mm³ enrolled in a multicenter nutritional supplementation trial. Baseline BCM, total body fat and extracellular mass as measured by bioelectrical impedance analysis, dietary intake (24h food recall) and muscle building activity assessed by structured interview were analyzed to determine association(s) between body composition variables and macronutrient intake. Multiple regression analysis showed that BCM was positively associated with body weight ($P < 0.001$), height ($P < 0.001$), protein intake ($P < 0.001$), muscle-building activity ($P < 0.001$) and African-American ethnicity ($P > 0.05$) and negatively associated with carbohydrate intake ($P < 0.05$), age ($P < 0.001$) and number of prior AIDS-related diagnoses ($P < 0.001$). We conclude that protein intake is associated with increased BCM, whereas carbohydrate intake is negatively associated with BCM in HIV-infected men, independently of muscle building activity.

Gibert CL, Wheeler DA, Collins D, Madans M, Muurahainen N, Raghavan SS, et al. Randomized, controlled trial of caloric supplements in HIV infection. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999;22:253-259.

The objective of the study was to compare the efficacy of three nutritional regimens in the prevention of weight loss. The design was a three-arm randomized, controlled trial with primary outcome measure percent change in weight over 4 months. There were no significant differences among the three regimens in the percent change in weight and body cell mass. The study concluded that caloric supplements do not promote increases in average weight or body cell mass in weight-stable, HIV-infected adults beyond that offered by a multivitamin and mineral supplement.

CPCRA 038-Nutrition, cont.

Muurahainen N, Mulligan K. Clinical trials update in Human Immunodeficiency Virus wasting. *Semin Oncol* 1998;25(6):104-111.

The major acquired immunodeficiency syndrome (AIDS) clinical trials groups in the Division of AIDS of the NIH have been investigating weight loss and wasting in persons with the human immunodeficiency virus (HIV) and AIDS. This article reviews multicenter trials concerning HIV-related malnutrition and wasting conducted by the AIDS clinical trials groups. CPCRA trials will examine the effects of caloric supplements and triglycerides, or the use of megestrol acetate, oxandrolone, and progressive resistance training, on weight loss in patients with HIV-associated wasting. Planned ACTG trials will study the effects of the combination of megestrol acetate and testosterone, the testosterone derivative nandrolone decanoate, or highly active antiretroviral therapy on weight loss. Results from these studies may also have relevance to clinical oncologists who are treating patients with cancer-related cachexia.

CPCRA 039-bis-POM

A Phase III, Randomized, Double blind, Placebo-controlled Study of the Safety and Efficacy of Adefovir Dipivoxil (bis-POM PMEA) in Prolonging Survival in HIV-infected Individuals with a CD4+ cell count of ≤ 100 cells/mm³ or a Lifetime Nadir of ≤ 50

Fisher EJ, Chaloner K, Cohn DL, Bjorling Grant L, Alston B, Brosgart CL, Schmetter B, El-Sadr WM, Sampson J. The safety and efficacy of adefovir dipivoxil in persons with advanced HIV disease: a randomized, prospective trial. *AIDS* 2001; 15:1695-1700.

Objective: Efficacy and safety of adefovir dipivoxil (adefovir) added to background antiretroviral therapy in advanced HIV disease. **Design:** Randomized, double blind, placebo-controlled trial. **Setting:** Multicenter clinical trials program. **Participants:** Adults with CD4+ cell count $\leq 100/\mu\text{L}$, or 101-200/ μL with prior nadir $\leq 50/\mu\text{L}$. **Interventions:** Oral adefovir or placebo 120 mg daily. **Primary outcome measures:** Survival, cytomegalovirus (CMV) disease. **Results:** Among the 253 patients assigned adefovir and the 252 assigned placebo, respectively, 17 and 16 died (relative risk=1.05; 95% CI: 0.53 to 2.09; p-value=0.88), and 4 and 8 experienced confirmed CMV disease (relative risk=0.49; 95% CI: 0.15 to 1.64; p-value=0.25. At 12 months the cumulative percent with nephrotoxicity was 17% in the adefovir group and 0.4% in the placebo group (log rank p-value<0.0001). Among patients assigned adefovir, median time to resolution of PRTD was 15 weeks, and 16% of patients did not resolve completely. There were no differences in grade 4 toxicities; significantly more drug discontinuations occurred in the adefovir group. **Conclusions:** Evaluation of clinical endpoints was inconclusive due to low event rates. A significantly higher rate of nephrotoxicity was observed in patients assigned adefovir. This study does not support the use of adefovir 120 mg daily for to prolong survival or prevent CMV disease in patients with advanced HIV disease.

CPCRA 042-NvR

A Randomized Trial of the Efficacy and Safety of a Strategy of Starting With Nelfinavir Versus Ritonavir Added to Background Antiretroviral Reverse Transcriptase Inhibitor Therapy in HIV-Infected Individuals With CD4+ Cell Counts $\leq 200/\text{mm}^3$

MacArthur R, Perez G, Walmsley S, Baxter J, Mullin C, Neaton J. Comparison of prognostic importance of latest CD4+ cell count and HIV RNA levels in patients with advanced HIV infection on highly active antiretroviral therapy. *HIV Clin Trials* 2005;6(3):127-135.

The comparative prognostic importance of latest plasma HIV RNA levels (viral loads) and CD4+ cell counts among patients prescribed highly active antiretroviral therapy (HAART) has not been well characterized. **Method:** We assessed the prognostic value of latest CD4+ cell counts and latest viral loads for progression to AIDS or death and explored their interaction among 432 HIV-infected persons with advanced HIV who were prescribed a protease inhibitor (PI) as their first HAART regimen. **Results:** Pre-HAART median CD4+ cell count and viral load were 41 cells/mm³ and 126,331 copies/mL, respectively. After 12 months of HAART, the median CD4+ cell count was 154 cells/mm³; 39% of patients had a viral load of 400 copies/mL or lower. Over a median follow-up of 33 months, 109 (25%) of the 432 patients experienced an AIDS event or died. The hazard ratio for AIDS or death for those with latest CD4+ cell count <50 cells/mm³ versus ≥ 200 cells/mm³ was 13.9 (95% CI 6.5 to 29.7) without adjustment for latest viral load measurements and 9.5 (95% CI 4.0 to 22.5) after adjustment for latest viral load. In contrast, the hazard ratio for AIDS or death for those with viral load $\geq 100,000$ versus <400 copies/mL was 4.2 (95% CI 2.3 to 7.7) without adjustment for

CPCRA 042-NvR, cont.

latest CD4+ level and 1.2 (95% CI 0.6 to 2.4) with adjustment for latest CD4+ cell count. **Conclusion:** We conclude that when latest CD4+ cell count and viral load are considered separately, both are significantly related to AIDS or death; when these markers are jointly considered, the association of viral load with AIDS or death is substantially diminished. Latest CD4+ levels are more strongly related to AIDS or death than latest viral load levels in patients on HAART.

Loutfy M, Walmsley S, Mullin C, Perez G, Neaton J. CD4+ increase predicts clinical benefit in patients with advanced HIV with persistent viremia after one year of combination antiretroviral therapy. *J Infect Dis* 2005(15 October);192:1407-1411.

The relationship between 12-month CD4+ cell count response and clinical outcome (AIDS-defining event or death) in a subset of 228 patients with human immunodeficiency virus load >400 copies/mL despite receiving combination antiretroviral therapy as part of a larger randomized trial was defined by use of Cox models. The 12-month CD4+ cell count responses were divided into 5 categories, ranging from decrease or no change (19% of patients) to a ≥ 100 -cell/mm³ increase (27% of patients). There was a lower risk of clinical progression for each incremental increase in CD4+ cell count response. A 25-cell/mm³ increase in CD4+ cell count was associated with a 21% reduction in the risk of an AIDS-defining event or death ($P < .0001$).

Perez G, MacArthur R, Walmsley S, Baxter J, Mullin C, Neaton J. A randomized clinical trial Comparing nelfinavir and ritonavir in patients with advanced HIV disease (CPCRA 042/CTN 102). *HIV Clin Trials* 2004;5(1):7-18.

Purpose: To compare the long-term clinical efficacy and toxicity of initial strategies of nelfinavir (NFV) or ritonavir (RTV) in patients with CD4+ cells below 200/mm³. **Method:** This was an open-label randomized multicenter trial (CPCRA, CTC). Patients were naïve to protease inhibitor use except for hard gel saquinavir. Patients who were intolerant to their assigned therapy were allowed to switch arms (later RTV-intolerant patients could switch to indinavir). The primary objective was to compare the regimens for AIDS-defining conditions and death (AIDS/death) using intent-to-treat analysis. Hazard ratios (HR) for NFV and RTV were estimated using Cox's proportional hazards models. Kaplan-Meier life table summaries were also used to compare the two groups. **Results:** There were 775 patients who were randomized beginning in January 1997 and followed through December 2001. At entry, mean CD4+ cell count was 58 cells/mm³ and the HIV RNA level averaged 4.9 log copies/mL. After a median follow-up of 52 months, rates of AIDS/death were 12.7 and 11.0 per 100 person years for the NFV and RTV groups, respectively (HR=1.16; 95% CI, 0.92-1.46; $p = .21$). Discontinuations occurred earlier in the RTV group ($p = .0001$). **Conclusion:** There are moderate differences in efficacy and large differences in tolerability between a strategy of initial NFV or RTV in patients with advanced disease. Finding the right balance between potency and tolerability remains a challenge. **Key words:** clinical endpoints, protease inhibitors, tolerability.

CPCRA 046-GART

A Pilot Study of the Short-Term Effects of Antiretroviral Management Based on Plasma Genotypic Antiretroviral Resistance Testing (GART) Compared With Antiretroviral Management Without Plasma GART

Baxter JD, Merigan TC, Wentworth DN, Neaton JD, Hoover ML, Hoetelmans RMW, et al. Both baseline HIV-1 drug resistance and antiretroviral drug levels are associated with short-term virological responses to salvage therapy. *AIDS* 2002; 16:1131-1138.

To determine the impact of HIV-1 drug resistance at baseline and antiretroviral drug levels (DL) during follow-up on virologic response to the next antiretroviral regimen. **Conclusions:** In salvage therapy, both the number of active drugs and the DL for each drug in the new regimen determine the antiviral response.

Weinstein MC, Goldie SJ, Losina E, Cohen CJ, Baxter JD, Zhang H, et al. Use of genotypic resistance testing to guide HIV therapy: Clinical impact and cost-effectiveness. *Ann Intern Med* 2001; 134:440-450.

To assess the cost-effectiveness of genotyping resistance testing for patients acquiring drug resistance through failed treatment (secondary resistance) and those infected with resistant virus (primary resistance). **Conclusions:** Genotypic antiretroviral resistance testing following antiretroviral failure is cost-effective. Primary resistance testing also seems to be reasonably cost-effective and will become more so as the prevalence of primary resistance increases.

CPCRA 046-GART, cont.

Winters MA, Baxter JD, Mayers DL, Wentworth DN, Hoover ML, Neaton JD, et al. Frequency of antiretroviral drug resistance mutations in HIV-1 strains from patients failing triple drug regimens. *Antiviral Ther* 2000, 5(1):57-63.

This paper describes a prospective randomized controlled trial (CPCRA 046) that determined the short-term effects of using genotypic antiretroviral resistance testing (GART) with expert advice in the management of patients failing on a protease inhibitor and two nucleoside reverse transcriptase inhibitors. 153 HIV-infected adults with a three-fold or greater rise in plasma HIV-1 RNA on at least 16 weeks of combination antiretroviral therapy were studied. Randomization was either to a GART group, where genotype interpretation and suggested regimens (the GART report) were provided to clinicians, or to a No-GART group, where treatment choices were made without such input. The primary endpoint was change in plasma HIV-1 RNA levels from baseline to the average of the 4 and 8 week levels. The average baseline CD4 cell count was 230 cells/mm³ and the median plasma HIV-1 RNA was 28,085 copies/mL. The number of drugs prescribed to which the patients' HIV-1 appeared susceptible (active drugs) was significantly greater in the GART compared with the No-GART group. The results showed that, in patients failing triple drug therapy, GART with expert advice was superior to No-GART as measured by short-term viral load responses.

Baxter JD, Mayers DL, Wentworth DN, Neaton JD, Hoover ML, Winters MA, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. *AIDS* 2000 14(9)F83-F93.

This paper describes the CPCRA 046 GART study, a randomized controlled trial to determine the short-term effects of using genotypic antiretroviral resistance testing (GART) with expert advice in the management of patients failing on a protease inhibitor and two nucleoside reverse transcriptase inhibitors. The study included 153 HIV-infected adults with a threefold or greater rise in plasma HIV-1 RNA on at least 16 weeks of combination antiretroviral therapy. Randomization was either to a GART group, where genotype interpretation and suggested regimens were provided to clinicians, or to a no-GART group, where treatment choices were made without such input. The average baseline CD4 cell count was 230×10^6 cells/l and the median HIV-1 RNA was 28,085 copies/ml. At entry, 82 patients were failing on regimens containing indinavir, 51 on nelfinavir, 11 on ritonavir, and nine on saquinavir. HIV-1 RNA, averaged at 4 and 8 weeks, decreased by $1.19 \log_{10}$ for the 78 GART patients and $-0.61 \log_{10}$ for the no-GART patients (treatment difference: $-0.53 \log$, 95% confidence interval), -0.77 to -0.29 ; $P=0.00001$). Overall, the best virologic responses occurred in patients who received three or more drugs to which their HIV-1 appeared to be susceptible. Conclusion: In patients failing triple drug therapy, GART with expert advice was superior to no-GART as measured by short-term viral load responses.

DeGruttola V, Dix L, D'Aquila R, Holder D, Phillips A, Ait-Khaled M, Baxter J, et al. The relation between baseline HIV drug resistance and response to antiretroviral therapy: re-analysis of retrospective and prospective studies using a standardized data analysis plan. *Antiviral Ther* 2000; 5:41-48.

To assess the relation between resistance to antiretroviral drugs for treatment of HIV-1 infection and virological response to therapy, results from 12 different studies were re-analysed according to a standard data analysis plan. These studies included nine clinical trials and three observational cohorts. The primary end-point in our analyses was virological failure by week 24. Baseline factors that were investigated as predictors of virological failure were plasma HIV-1 RNA, the number and type of new antiretroviral drugs in the regimen, and viral susceptibility to the drugs in the regimen, determined by genotyping or phenotyping methods. These analyses confirmed the importance of both genotypic and phenotypic drug resistance as predictors of virological failure, whether these factors were analysed separately or adjusted for other baseline confounding factors. In most of the re-analysed studies, the odds of virological failure were reduced by about twofold for each additional drug in the regimen to which the patient's virus was sensitive by genotyping methods, and by about two-to threefold for each additional drug that was sensitive by phenotyping.

CPCRA 048-CR-MAC

A Randomized, Double-Blind, Placebo-Controlled Trial of Prophylaxis for Disseminated *Mycobacterium avium* Complex Disease and Bacterial Pneumonia Versus Deferred= Prophylaxis in HIV-Infected Patients Who Experience Rebound in CD4+ Cell Count Due to Active Antiretroviral Therapy

EI-Sadr WM, Burman WJ, Bjorling Grant L, Matts JP, Hafner R, Crane L, et al. Discontinuation of prophylaxis against *Mycobacterium avium* complex in HIV-infected patients who have a response to antiretroviral therapy. *N Engl J Med* 2000;342(15):1085-1092.

This paper describes a multicenter, double-blind, randomized trial comparing azithromycin with placebo among patients whose CD4+ cell count increased from <50 to >100 cell/mm³ with antiretroviral therapy. The primary endpoint of the trial was disseminated MAC or bacterial pneumonia. A total of 520 patients were enrolled in the study; 65% had a prior AIDS-defining illness; the results showed that there were no episodes of disseminated MAC in either treatment group. In addition, there was no difference in the rates of disseminated MAC or bacterial pneumonia in the azithromycin or placebo arms of the study. The study demonstrated that deferral or withdrawal of azithromycin prophylaxis is safe among HIV-infected patients who have experienced CD4+ cell rebound to >100 cells/mm³ due to antiretroviral therapy. This policy can simplify treatment regimens, decrease adverse events, decrease risk of antimicrobial resistance and may improve adherence to other therapies.

CPCRA 058-FIRST

A Randomized, Open-Label Study of the Long-Term Effectiveness of Three Initial Highly Active Antiretroviral Therapy (HAART) Strategies in HAART-Naive, HIV-Infected Persons

MacArthur RD, Novak RM, Peng G, Chen L, Xiang Y, Huppler Hullsiek K, Kozal MJ, Van den Berg-Wolf M, Henely C, Schmetter B, Dehlinger M. Long-Term Clinical and Immunologic Outcomes Are Similar in HIV-Infected Persons Randomized to NNRTI vs PI vs NNRTI+PI-based Antiretroviral Regimens as Initial Therapy: Results of the CPCRA 058 FIRST Study. *The Lancet* December 16, 2006;368:2125-2135.

Editorial: Abgrall S. Initial strategy for antiretroviral-naïve patients. *The Lancet* December 16, 2006;368:2107-2109

Background: Long-term data from randomized trials on the consequences of treatment with a protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or both are lacking. Here, we report results from the FIRST trial, which compared initial treatment strategies for clinical, immunological, and virological outcomes. **Methods:** Between 1999 and 2002, 1397 antiretroviral-treatment-naïve patients, presenting at 18 clinical trial units with 80 research sites in the SUA, were randomly assigned in a ratio of 1:1:1 to a protease inhibitor (PI) strategy (PI plus nucleoside reverse transcriptase inhibitor [NRTI]; n=470), a non-nucleoside reverse transcriptase inhibitor (NNRTI) strategy (NNRTI plus NRTI; n=463), or a three-class strategy (PI plus NNRTI; n=464). Primary endpoints were a composite of an AIDS-defining event, death, or CD4 cell count decline to less than 200 cells per mm³ for the PI versus NNRTI comparison and average change in CD4 cell count at or after 32 months for the three-class versus combined two-class comparison. Analyses were by intention-to-treat. This study is registered with ClinicalTrials.gov, number NCT00000922. **Findings:** 1397 patients were assessed for the composite endpoint. A total of 388 participants developed the composite endpoint, 302 developed AIDS or died, and 188 died. NNRTI versus PI hazard ratios (HRs) for the composite endpoint, for AIDS or death, for death, and for virological failure were 1.02 (95% CI 0.79-1.31), 1.07 (0.80-1.41), 0.95 (0.66-1.37), and 0.66 (0.56-0.78), respectively. 1196 patients were assessed for the three-class versus combined two-class primary endpoint. Mean change in CD4 cell count at or after 32 months was +234 cells per mm³ and +227 cells per mm³ for the three-class and the combined two-class strategies (p=0.62), respectively. HRs (three-class vs combined two-class) for AIDS or death and virological failure were 1.15 (0.91-1.45) and 0.87 (0.75-1.00), respectively. HRs (three-class vs combined two-class) for AIDS or death were similar for participants with baseline CD4 cell counts of 200 cells per mm³ or less and of more than 200 cells per mm³ (p=0.38 for interaction), and for participants with baseline HIV RNA concentrations less than 100000 copies per mL and 1000000 copies per mL or more (p=0.26 for interaction). Participants assigned the three-class strategy were significantly more likely to discontinue treatment because of toxic effects than were those assigned to the two-class strategies (HR 1.58; p<0.0001). **Interpretation:** Initial treatment with either an NNRTI-based regimen or a PI-based regimen, but not both together, is a good strategy for long-term antiretroviral management in treatment-naïve patients with HIV.

CPCRA 058-FIRST, cont.

Novak RM, Chen L, MacArthur RD, Baxter JD, Huppler Hullsiek K, Peng G, Xiang Y, Henely C, Schmetter B, Uy J, van den Berg-Wolf M, Kozal M, and the Terry Beirn Community Programs for Clinical Research on AIDS 058 Study Team. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naïve patients: implications for routine resistance screening before initiation of antiretroviral therapy. *Clin Infect Dis* 2005; 40:468-474.

Background: The prevalence of drug resistance among persons with newly acquired human immunodeficiency virus (HIV) infection is well documented. However, it is unclear to what extent these mutations persist in chronically infected, treatment-naïve patients. **Methods:** Prevalence of and factors associated with genotypic drug resistance were analyzed retrospectively in a subset of 491 chronically HIV-infected, antiretroviral-naïve patients enrolled at 25 sites in the Terry Beirn Community Programs for Clinical Research on Acquired Immune Deficiency Syndrome (AIDS) Flexible Initial Retrovirus Suppressive Therapies trial during 1999-2001. Resistance was defined on the basis of the International AIDS Society 2003 definition, as well as the presence of additional mutations at codons 215 (C/D/E/S) and 69 (A.N.S) in the *pol* gene. Prevalence of mutations was estimated by use of techniques for stratified random samples. Logistic regression models were used to determine factors associated with resistance. **Results:** Among the 491 chronically HIV-infected patients (mean CD4 cell count, 269 cells/mm³; 31% of patients had a prior AIDS diagnosis), 57 (11.6%) had ≥1 resistance mutation, resulting in an estimated prevalence for the cohort of 10.8% (95% confidence interval [CI], 9.5%-12.1%). The prevalence was 8.8% if the 118I mutation was excluded. By drug class, the estimated prevalence of mutations conferring resistance to nucleoside reverse-transcriptase inhibitors was 7.8% and the prevalence was 3.0% for nonnucleoside reverse-transcriptase inhibitors and 0.7% for protease inhibitors. In a multiple logistic regression analysis, non-Hispanic white subjects were twice as likely than African American subjects to have resistance (odds ratio [OR], 2.1; 95% CI, 1.1-4.1; *P* = .03), and there was a 40% increase per year in prevalence of mutations by later year of enrollment (OR, 1.4; 95% CI, 1.0-2.1; *P* = .05). **Conclusions:** These results demonstrate the persistence of drug resistance mutations in chronically HIV-infected patients and an increasing prevalence of resistance over time, and they support genotyping of virus at baseline for chronically HIV-infected patients.

MacArthur RD, Chen L, Peng G, Novak RM, van den Berg-Wolf M, Kozal M, Besch L, Yurik T, Schmetter B, Henely C, Dehlinger M and the CPCRA 058 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. Efficacy and safety of abacavir plus lamivudine versus didanosine plus stavudine when combined with a protease inhibitor, a non-nucleoside reverse transcriptase inhibitor, or both in HIV-1 positive antiretroviral-naïve persons. *HIV Clin Trials* 2004; 5(6):361-370.

Purpose: The combination of abacavir + lamivudine (ABC+3TC) versus didanosine + stavudine (ddI+ddT), each combined with other classes of antiretrovirals (ARVs) in ARV-naïve patients, was compared for the combined endpoint of time to plasma HIV RNA >50 copies/mL (at or after the 8-month visit) or death (primary endpoint) in a nested substudy of an ongoing multicenter randomized trial. **Method:** The substudy enrolled 182 patients; mean HIV RNA and CD4+ cell counts at baseline were 5.1 log₁₀ copies/mL and 212 cells/mm³, respectively. **Results:** After a median follow-up of 28 months, rates of primary endpoint were 57.2 and 67.8 per 100 person-years for the ABC+3TC and ddI+ddT groups (hazard ratio [HR] = 0.81, 95% confidence interval [CI] 0.58-1.14, *p* = .23). **Conclusion:** There was a trend for treatments containing ABC+3TC to be better than treatments containing ddI+ddT with respect to HIV RNA decreases, CD4+ cell count increases, and tolerability.

MacArthur RD, Chen L, Mayers DL, Besch CL, Novak R, van den Berg-Wolf M, et al. The rationale and design of the CPCRA (Terry Beirn Community Programs for Clinical Research on AIDS) 058 FIRST (Flexible Initial Retrovirus Suppressive Therapies) Trial. *Control Clin Trials* 2001; 22: 176-190.

The CPCRA 058 FIRST (Flexible Initial Retrovirus Suppressive Therapies) trial is a large, long-term randomized, prospective comparison of three different antiretroviral strategies in highly active antiretroviral therapy-naïve, HIV-1-infected persons. The trial was designed as a flexible framework upon which other studies could be added to answer more limited, but still important, questions. This article presents the study design, discusses the challenges we have faced in implementing the trial, and describes our preliminary experiences.

CPCRA 059-IL-2

A Randomized, Open-Label, Study of the Impact of Two Doses of Subcutaneous Recombinant IL-2 (Proleukin[®]) on Viral Burden and CD4⁺ Cell Count in Patients With HIV-1 Infection and CD4⁺ Cell Counts $\geq 300/\text{mm}^3$

Markowitz N, Bebhuk J, Abrams D. Nadir CD4⁺ t-cell count predicts response to subcutaneous recombinant interleukin-2. *Clin Infect Dis* 2003;37:e115-120.

Community Program for Clinical Research on AIDS 059 was a multicenter study conducted among human immunodeficiency virus (HIV)-infected individuals with CD4⁺ cell counts ≥ 300 cells/mm³ who were randomly assigned to receive antiretroviral therapy with or without intermittent subcutaneously administered recombinant interleukin-2 (rIL-2). To identify factors associated with a response to IL-2, a secondary analysis was performed that included the subset of rIL-2 recipients who were able to complete all 3 initial treatment cycles. Predictors of a change in CD4⁺ cell count between baseline and month after the start of treatment cycle 3 were examined in a multivariate model that included sex, race, body surface area, rIL-2 dose, HIV load, and both baseline and nadir CD4⁺ cell count. The combination of race and sex ($P = .027$) and the nadir CD4⁺ cell count ($P = .05$) were significant predictors of mean CD4⁺ cell count response. Baseline CD4⁺ cell count had no significant effect. The strong association between nadir CD4⁺ cell count and CD4⁺ cell count response suggest that immunologic losses resulting from HIV-mediated CD4⁺ cell depletion may be irreversible.

Abrams DI, Bebhuk JD, Denning ET, Davey RT, Fox L, Lane HC, Sampson J, Verheggen R, Zeh D, Markowitz NP. Randomized open-label study of the impact of two doses of subcutaneous recombinant Interleukin-2 on viral burden in patients with HIV-1 infection and CD4⁺ cell counts $\geq 300/\text{mm}^3$: CPCRA 059. *J Acquir Immune Defic Syndr Hum Retrovirol* 2002; 29:221-231.

The effect of intermittent courses of recombinant interleukin-2 (rIL-2) on HIV-1 load in patients receiving combination antiretroviral therapy remains uncertain. CPCRA 059 was an open-label, randomized, multicenter trial in which 511 patients with HIV-1 infection and CD4⁺ cell counts of $\geq 300/\text{mm}^3$ who were receiving antiretroviral therapy were assigned to receive no rIL-2 (255 patients [controls]) or subcutaneous rIL-2 in dosages of 4.5 MIU (130) or 7.5 MIU (126) twice daily for 5-day courses every 8 weeks to maintain CD4⁺ cell counts that were twice the baseline value or $\geq 1,000/\text{mm}^3$. The primary objective of this study was to compare the effects of the two doses of rIL-2 and no rIL-2 on viral load and CD4⁺ cell counts over 12 months. There was no difference in the following viral load measurements between the rIL-2 treatment groups and the control treatment group: percentage of patients with viral loads of <50 copies/mL at 12 months ($p = .55$), time to viral load of ≥ 5 copies/mL for patients who had baseline viral loads of <50 copies/mL ($p = .35$), and change in viral load from baseline for patients who had viral loads of ≥ 50 copies/mL at baseline ($p = .63$). At each follow-up visit, the change in CD4⁺ cell count from baseline was significantly greater in the rIL-2 treatment groups than in the control treatment group, with a mean difference of $251/\text{mm}^3$ at month 12 (95% confidence interval, 207-295; $P < .0001$). No unanticipated adverse experiences were seen in this trial, to our knowledge the largest randomized evaluation of rIL-2 treatment conducted to date.

CPCRA 061-Metabolic

Metabolic Consequences of Highly Active Antiretroviral Therapy (HAART) in HIV-Positive Individuals

Visnegarwala F, Raghavan SS, Mullin CM, Bartsch G, Wang J, Kotler D, Gibert CL, Shlay J, Grunfeld C, Carr A, El-Sadr W. Sex differences in the associations of HIV disease characteristics and body composition in antiretroviral-naive persons. *Am J Clin Nutr* 2005 October; 82(4):850-856.

Background: Data on associations of body composition with HIV disease characteristics are limited. **Objective:** We compared sex-specific associations between HIV disease characteristics and body composition in a racially-ethnically diverse cohort of antiretroviral-naive patients. **Design:** The study was a cross-sectional analysis of participants enrolled in a metabolic substudy of a multicenter trial. Regional fat was measured, and total body fat (TBF) was derived by using the Durnin-Womersley formula (DWF) and bioelectrical impedance analysis (BIA). Body cell mass (BCM) was measured by BIA. **Results:** Among 422 participants, 22% were women, 60% were African American, and 36% had prior AIDS-defining illnesses. Mean (\pm SD) age was 38.2 ± 9.6 y, CD4⁺ count was 215 ± 184 cells/mm³, and HIV RNA log₁₀ was 5.0 ± 0.8 copies/mL. On multivariate analysis, women with AIDS-defining illness had significantly ($P < 0.005$) lower regional body fat and TBF (BIA: -9.5 kg; DWF: -7.3 kg) but nonsignificantly lower BCM (-1.3 kg) than did women without such illnesses, whereas men with AIDS-defining illness had significantly ($P < 0.005$) lower BCM (-1.7 kg) but nonsignificantly lower TBF (BIA: -1.3 kg; DWF: -1.83 kg) than did men without such illnesses ($P < 0.05$ for sex differences in TBF). Significant negative associations of HIV RNA with BCM (-0.9 kg/log RNA; $P = 0.03$), TBF by BIA (-1.4

CPCRA 061-Metabolic, cont.

kg/log RNA; $P = 0.05$) and by DWF (-1.6 kg/log RNA; $P = 0.01$), and regional fat were observed in men only. **Conclusions:** The effect of prior AIDS illness on body fat differed significantly between the sexes: women with prior AIDS-defining illness had significantly less fat than did women without such illnesses. An independent effect of HIV viremia on BCM and fat was seen in men. These distinctions may be due to inherent biological differences between the sexes.

El-Sadr WM, Mullin CM, Carr A, Gibert C, Rappoport C, Visnegarala F, Grunfeld C, Raghavan SS. Effects of HIV disease on lipid, glucose and insulin levels: results from a large antiretroviral-naïve cohort. *HIV Medicine* 2005;6:114-121.

Objectives. With the use of potent antiretroviral therapy in patients with HIV disease, changes in lipid parameters and glucose homeostasis have been onte. Hover, these effects have been difficult to interpret because of the varied demographic and treatment characteristics of the cohorts and the complexity of difrentiating the effect of HIV disease from that of the drugs used in its treatment. This study was designed to explore these issues. **Methods.** Demographic information and fasting blood samples were collected from 419 antiretroviral-naïve HIV-1-infected patients.

Conclusions. Both HIV disease and demographic characteristics were found to influence lipid values and glucose homeostasis in the absence of antiretroviral treatment. More advanced HIV disease was associated with less favourable lipid and glucose homeostatic profiles. The independent association between HIV RNA levels and various lipid parameters suggests that viral replication had a direct effect on lipid levels. Interpretation of the effects of various HIV treatment regimen and drugs on metabolic parameters must take into account the stage of HIV disease and the demographic characteristics of the population studied.

Shlay JC, Visnegarwala F, Bartsch G, Wang J, Peng G, El-Sadr WM, Gibert C, Kotler D, Grunfeld C, and Raghavan S for the Terry Beirn Community Programs for Clinical Research on AIDS. Body composition and metabolic changes in antiretroviral-naïve patients randomized to didanosine and stavudine vs. abacavir and lamivudine. *J Acquir Immune Defic Syndr* 2005; 38(2):147-155.

Comparisons of body composition and metabolic changes among antiretroviral-naïve patients randomly assigned to didanosine and stavudine- (ddI+d4T vs. abacavir and lamivudine- (ABC+3TC) containing regimens were assessed in a nested substudy of an ongoing multicenter randomized trial. At baseline and every 4 months, body cell mass and total body fat were calculated, anthropometric measurements were performed, and fasting metabolic parameters were obtained. The rates of change (unit/mo) estimated using the slopes of regression lines and overall mean changes from baseline were compare by study assignment. Among 9 patients enrolled, 46 received ddI+d4T- and 50 received ABC+3TC-containing regimens with a median follow-up of 32.4 months. For both study arms, an overall increase in the rates of change was seen for body cell mass. For ddI+d4T, after an initial increase, the rates of change declined for regional fat and total body fat compared with an increase for ABC+3TC, with the 2 arms being significantly different ($P < 0.05$). For high-density lipoprotein cholesterol rates of change, ddI+d4T decreased, while ABC+3TC increased. For both arms, low-density lipoprotein cholesterol decreased, while triglycerides increased. Early and sustained increases in insulin and insulin resistance were seen only for ddI+d4T. In this prospective study, metabolic and body composition changes varied according to whether subject received ddI+d4T or ABC+3TC.

Wang J, Bartsch G, Raghavan SS, Yurik T, Peng G, Chen L, LeSueur D, Shlay J for the Terry Beirn Community Programs for Clinical Research on AIDS. Reliability of circumferences and skinfold measurements by 19 observers trained in groups. *Int J Body Composition Res* 2004; 2(1):31-36.

Background: Waist circumference (WC) is now accepted as a practical measure of adipose tissue distribution. Four body sites for WC measurements are commonly used, as follows: immediately below the lowest ribs (WC1), the narrowest waist (WC2, and midpoint between the lowest rib and the iliac crest (WC3), and immediately above the iliac crest (WC4). **Objective:** We sought to compare the magnitude and reliability of WC measured at these 4 sites in males and females. **Design:** WC was measured at each site 1 time in all subjects [49 males and 62 females, aged 7-83 y, with a body mass index (in kg/m^2) of 9-43] and 3 times in a subgroup ($n = 93$) by one experienced observer using a heavy-duty inelastic tape. Body fat was measured in a subgroup ($n = 74$) with the use of dual-energy X-ray absorptiometry. **Results:** The mean values of WC were $\text{WC2} < \text{WCX1} < \text{WC3} < \text{WC4}$ ($P < 0.01$) in females and $\text{WC2} < \text{wc1}, \text{WC3}, \text{and WC4}$ ($P < 0.01$) in males. For all 4 sites, measurement reproducibility was high, with intraclass correlation (r) values ≥ 0.99 . WC values were significantly correlated with fatness; correlations with trunk fat were higher than correlations with total body fat in both sexes. **Conclusions:** WC values at the 4 commonly used anatomic sites differ in magnitude depending on sex, are highly reproducible, and are correlated with total body and trunk adiposity in a sex-dependent manner. These observations have implications for the use of WC measurements in clinical practice and patient-oriented research.

CPCRA 062-Adherence

Adherence Strategies Using a Medication Manager and an Electronic Medication Reminder System for HIV-Infected Patients Receiving HAART

Mannheimer SB, Morse E, Matts JP, Andrews L, Child C, Schmetter B, Friedland GH. Sustained benefit From a Long-Term Antiretroviral Adherence Intervention. *J Acquir Immune Defic Syndr* December 1, 2006;43:S41-S47.

Objective: To assess the efficacy of 2 adherence interventions, medication managers (MM) and medication alarms (ALR), among antiretroviral (ARV)-naïve persons with HIV initiating ARV therapy. **Methods:** A multicenter, randomized, adherence intervention clinical trial was conducted among participants coenrolled in an HIV ARV strategy study for ARV-naïve individuals. Sites were assigned by cluster randomization using a 2x2 factorial design to administer MM, ALR, MM+ALR, or neither (control). MM participants received individualized, structured, long-term adherence support from trained MMs. ALR participants received individually programmed ALR alarms for use throughout the study. **Results:** The 928 participants, followed a median of 30 months, included 22% women and 75% nonwhites; the median baseline CD4 count was 155 cells/mm³. First virologic failure was 13% lower in all MM versus no-MM groups ($P=0.13$) and 28% lower in MM versus non-MM subgroups randomized to 2-class ARV arms in the parent ARV study ($P=0.01$). MM (vs. no-MM) participants had significantly better CD4 cells count ($P=0.01$) and adherence ($P<0.001$) outcomes. ALR (vs. no-ALR) participants had worse virologic outcomes. **Conclusion:** This large randomized clinical trial demonstrated that interpersonal structured adherence support was associated with improved long-term medication adherence and virologic and immunologic HIV outcomes. **Key Words:** adherence, alarm, antiretroviral therapy, behavior, HIV, intervention study.

Mannheimer SB, Matts J, Telzak E, Chesney M, Child C, Wu AW, Friedland G for the Terry Beinr Community Programs for Clinical Research on AIDS. Quality of life in HIV-infected individuals receiving antiretroviral therapy is related to adherence. *AIDS Care* 2005; 17(1):10-22.

This study assesses changes in quality of life (QoL) over time among HIV-infected individuals receiving antiretroviral therapy (ART) and evaluates how this relates to ART adherence. Prospective, longitudinal data were examined from 1050 participants in two large, randomized, multi-centre antiretroviral clinical trials. QoL was assessed by the SF-12; adherence by the Terry Beinr Community Programs for Clinical Research on AIDS Antiretroviral Medication Self-report. Participants included 20% women, 53% African Americans, 16% Latinos; mean age was 39 years; mean baseline CD4+ cell count 230 cells/mm³; 89% were ART-naïve at entry. Baseline physical and mental health summary QoL scores were 45.4 and 42.9, comparable to scores reported in other advanced HIV populations. Significant improvements in mean QoL scores were seen for the group as a whole after 1 to 4 months on new ART regimens, and persisted for 12 months. Participants reporting 100% ART adherence achieved significantly higher QoL scores at 12 months compared to those with poorer adherence, particularly if 100% adherence was consistent ($p < 0.001$). Those with at least 80% ART adherence had smaller gains in QoL at 12 months when compared to baseline, while those with <80% adherence had worsening of QoL. In this analysis, ART adherence was associated with improved QoL, particularly if adherence was sustained.

CPCRA 064-MDR-HIV

A Randomized Study of a Prescribed 4-Month Structured Treatment Interruption (STI) Followed by Initiation of a New Antiretroviral Regimen Versus Immediate Initiation of a New Antiretroviral Regimen In HIV-Infected Patients with Multidrug Resistant (MDR) Virus

Lawrence J, Huppler Hullsiek K, Thackeray LM, Abrams DI, Crane LR, Mayers DL, Jones MC, Saldanha JM, Schmetter BS, Baxter JD. Disadvantages of structured treatment interruption persists in patients with multidrug-resistant HIV-1: Final results of the the CPCRA 064 study. *J Acquir Immune Defic Syndr* October 1, 2006;43(2):169-178.

Background: We report the final results of Community Programs for Clinical Research on AIDS (CPCRA-064) study, a multicenter, prospective, randomized, controlled trial that determines the long-term clinical impact of structured treatment interruption (STI) in patients with multidrug-resistant (MDR) HIV-1. **Methods and Results:** Two hundred seventy-four patients on stable antiretroviral therapy with MDR HIV-1 treatment failure were randomized to a 4-month STI, followed by an optimized antiretroviral regimen (STI arm, n=140) or an immediate change to an optimized antiretroviral regimen (control arm, n=134). Main outcome measures were progression of disease or death and changes from baseline in HIV RNA levels (log copies/mL) and CD4 cell counts (cells/mm³). The median baseline HIV RNA level was 5.0 log copies/mL, the median CD4 count was 147 cells/mm³, and the nadir CD4 count was 32 cells/mm³. The median follow-up was 37 months. After the STI period, there were no differences

in

CPCRA 064-MDR-HIV, cont.

HIV RNA level responses between treatment arms. Differences in CD4 count responses always favored the control arm, with an advantage of 84 cells from 0 to 4 months ($P<0.0001$), 50 cells from 4 to 12 months ($P<0.0001$), 45 cells from 12 to 24 months ($P=0.006$), and 43 cells after 24 months ($P=0.07$). Rates in the STI and control arms for first progression-of-disease event or death were 17.5 and 14.3, respectively (hazard ratio=1.28; $P=0.22$). **Conclusion:** STI before changing regimens in patients with MDR HIV-1 treatment failure has a prolonged negative impact on CD4 cell count recovery and does not confer progression of disease or virologic benefits. **Key Words:** HIV Infection, salvage therapy, treatment failure, treatment interruption

Lawrence J, Mayers D, Huppler Hullsiek K, Gollins G, Abrams D, Reisler R, et al. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. *N Engl J Med* 2003; 349(9):837-46.

Prescribed interruptions in antiretroviral therapy--so-called "drug holidays"--may hasten disease progression in a subset of HIV-infected individuals, namely those whose treatment has been rendered significantly less effective by the development of resistance to multiple anti-HIV drugs (MDR-HIV).

CPCRA 065-SMART

A Large, Simple Trial Comparing Two Strategies for Management of Anti-Retroviral Therapy (The SMART Study)

El-Sadr WM, Lundren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, Babiker A, Burman W, Clumeck N, Cohen CJ, Cohn D, Cooper D, Darbyshire J, Emery S, Fätkenheuer G, Gazzard B, Grund B, Hoy J, Klingman K, Losso M, Ramos Mejia JM, Markowitz N, Neuhaus J, Phillips A, Rappport C. CD4+ Count-Guided Interruption of Antiretroviral Treatment. *NEJM* 2006;355(22):2283-2296.

Editorial: Currier JS, Baden LR. Getting Smarter – The Toxicity of Undertreated HIV Infection. *NEJM* 2006;25(22)2359-2361.

Background. Despite declines in morbidity and mortality with the use of combination antiretroviral therapy, its effectiveness is limited by adverse events, problems with adherence, and resistance of the human immunodeficiency virus (HIV). **Methods.** We randomly assigned persons infected with HIV who had a CD4+ count of more than 350 cubic millimeter to the continuous use of antiretroviral therapy (the viral suppression group) or the episodic use of antiretroviral therapy (the drug conservation group). Episodic use involved the deferral of therapy until the CD4+ count decreased to less than 250 per cubic millimeter and then the use of therapy until the CD4+ count increased to more than 350 per cubic millimeter. The primary end point was the development of an opportunistic disease or death from any cause. An important secondary end point was major cardiovascular, renal, or hepatic disease. **Results.** A total of 5472 participants (2720 assigned to drug conservation and 2752 to viral suppression) were followed for an average of 16 months before the protocol was modified for the drug conservation group. At baseline, the median and nadir CD4+ counts were 597 per cubic millimeter and 250 per cubic millimeter, respectively, and 71.7% of participants had plasma HIV RNA levels of 400 copies or less per milliliter. Opportunistic disease or death from any cause occurred in 120 participants (3.3 events per 100 person-years) in the drug conservation group and 47 participants (1.3 per 100 person-years) in the viral suppression group (hazard ratio for the drug conservation group vs. the viral suppression group, 2.6; 95% confidence interval [CI], 1.9 to 3.7; $P<0.001$). Hazard ratios for death from any cause and for major cardiovascular, renal, and hepatic disease were 1.8 (95% CI, 1.2 to 2.9; $P=0.007$) and 1.7 (95% CI, 1.1 to 2.5; $P=0.009$), respectively. Adjustment for the latest CD4+ count and HIV RNA level (as time-updated covariates) reduced the hazard ratio for the primary end point from 2.6 to 1.5 (95% CI, 1.0 to 2.1). **Conclusions.** Episodic antiretroviral therapy guided by the CD4+ count, as used in our study, significantly increased the risk of opportunistic disease or death from any cause, as compared with continuous antiretroviral therapy, largely as a consequence of lowering the CD4+ cell count and increasing the viral load. Episodic antiretroviral therapy does not reduce the risk of adverse events that have been associated with antiretroviral therapy.

Ellis KJ, Grund B, Visnegarwala F, Thackeray L, Miller CG, Chesson CE, El-Sadr W, Carr A. Visceral and Subcutaneous Adiposity Measurements in Adults: Influence of Measurement Site. *Intl J Obesity* (in press).

CPCRA Cross-Protocol Articles

Brar I, Shuter J, Thomas A, Daniels E, Absalon J. A comparison of factors associated with prevalent diabetes mellitus among HIV-infected antiretroviral (ART) naïve individuals versus individuals in the National Health and Nutritional Examination Survey (NHANES) Cohort. *J Acquir Immune Defic Syndr*

Background: In the general population, diabetes mellitus (DM) is associated with age, minority race/ethnicity, and obesity. Among HIV-infected persons, ART use and hepatitis C virus (HCV) infection have been associated with DM. This study examined DM prevalence and its predictors in ART-naïve HIV-infected patients. **Methods:** Cross-sectional analysis of ART-naïve HIV-infected adults enrolled in three CPCRA clinical trials versus adults enrolled in NHANES. **Results:** Prevalence of DM in CPCRA versus NHANES was 3.3% versus 4.8%. Mean BMI was lower in CPCRA versus NHANES (25 kg/m² versus 28 kg/m²). HCV was associated with DM only in univariate analyses in CPCRA. In both univariate and multivariate analyses, race/ethnicity, age and BMI were associated with DM in both cohorts. Among women, age and BMI were associated with DM in both cohorts. Among men, age and BMI were associated with DM in both cohorts; race/ethnicity was associated with DM only in NHANES. HCV was predictive of DM in blacks in CPCRA ($p=0.004$ before adjustment for multiple comparisons), but not in the full cohort. **Conclusion:** Our findings did not suggest an increased prevalence of DM in ART-naïve HIV-infected patients. While there was a trend toward increased prevalence of DM in HIV/HCV coinfecting patients, dominant risk factors associated with DM among ART-naïve HIV adults mirrored those of the general population.

Kozal M, Huppler Hullsiek K, Leduc R, Novak R, MacArthur R, Lawrence J, Baxter J. Prevalence and impact of HIV-1 protease codon 33 mutations and polymorphisms in treatment-naïve and treatment-experienced patients enrolling in clinical trials. *Antivir Ther* (anticipated June 2006).

Gibert C, Bartsch G, El-Sadr W, Shlay J, Peng G, Wang J, Visnegarwala F, Carr A, Raghavan S. Association between stage of HIV disease and self-perceived changes in body appearance. *Int J Body Comp Res* December 2005;3(4):133-129. Editorial included.

Many HIV-infected patients report a change in body appearance. A 'Change in Body Appearance' questionnaire, previously validated, was used to assess self-perceived changes in body appearance over the four months before enrollment into a clinical trial of antiretroviral-naïve HIV-infected patients. Seven hundred seventy-nine patients completed the questionnaire. Associations by gender, age, race, prior AIDS-defining illness, log₁₀ HIV RNA, and CD4+ lymphocyte count, with self-perception of changes in body size at seven sites, were determined. Median age was 38 years, 54% were African-American, 21.2% women, and 40% had a prior AIDS-defining illness. A higher proportion of men reported thinning of the arms, while a higher proportion of women reported a decrease in size of breast and buttocks. Comparing men with or without a prior AIDS-defining illness, those with a prior AIDS diagnosis reported a higher frequency of thinning at six sites. For men, prior AIDS diagnosis and a lower CD4+ lymphocyte count were independently associated with perceived loss of body size at six sites. While for women no association with prior AIDS was noted and a lower CD4+ lymphocyte count was only associated with smaller buttocks. With advanced HIV disease, men and women had different perceptions of change in body appearance. Overall, the questionnaire identified changes in body appearance for men and would be clinically useful to monitor self-perceived changes in body appearance of antiretroviral-naïve men.

Visnegarwala F, Chen L, Raghavan S, Tedaldi E for the Terry Bein Community Programs for Clinical Research on AIDS. Prevalence of diabetes mellitus and dyslipidemia among antiretroviral naïve patients co-infected with hepatitis C virus (HCV) and HIV-1 compared to patients without co-infection. *J Infection* 2005; 50(4):331-337.

Objective. An increased prevalence of type 2 diabetes mellitus (DM) has been associated with HCV in the non-HIV infected populations. To describe a similar association among HIV subjects, and explore the biological mechanisms. **Methods.** In a cross-sectional analysis, we compared the prevalence of DM (using American Diabetes Association criteria) and insulin resistance (HOMA IR) and dyslipidemia among ARV naïve patients with HIV and HIV/HCV infected patients enrolled in CPCRA FIRST (058) and the Metabolic Substudy (061). **Results.** Among 1389 enrolled in the FIRST study and had HCV serology, the prevalence of diabetes was higher (5.9%) among HCV/HIV as compared to 3.3% among those with HIV alone ($p=0.04$). Among 417 enrolled in the metabolic substudy, 88 (21%) had HIV/HCV co-infection. As in the main study, the prevalence of DM was higher in HIV/HCV group (9 vs. 3%, $p=0.03$). The HIV/HCV infected were significantly older (43 vs. 37 years), non-white (83 vs. 70%), with a history of IDU (55 vs. 3%), had higher AST (61 vs. 39 U/l), ALT (55 vs. 43 U/l), and lower cholesterol levels (3.97 vs. 4.25 mmol/l). By multivariate analysis among subjects <50 years, association between HCV and diabetes remained significant after adjusting for BMI, family history of diabetes (OR=3.7, 95% CI: 1.3–11.1, $p=0.02$). The insulin resistance (HOMA IR) was not different between the two groups, however, the prevalence of dyslipidemia was lower among HCV co-infected subjects. **Conclusions.** Subjects with HIV/HCV co-infection have a higher prevalence of diabetes and thus may need to be screened for it prior to initiation of anti-retroviral therapy, particularly if it is a PI based regimen.

CPCRA Cross-Protocol Articles, cont.

Tedaldi EM, Chen L, Markowitz N, Kelly L, Abrams D, the CPCRA Hepatitis Working Group. Effect of IL-2 on hepatitis C virus RNA levels in patients co-infected with human immunodeficiency virus receiving HAART. *J Viral Hepat* 2005 July; 12(4):414-20.

The effect of interleukin-2 (IL-2) on the plasma levels of hepatitis C RNA (HCV-RNA) has varied in published reports. We measured the impact of IL-2 on plasma HCV RNA levels in 54 human immunodeficiency virus (HIV)/HCV coinfected patients enrolled in a randomized trial of 512 participants designed to compare the virologic and immunologic effects of cycled IL-2 plus antiretroviral therapy (ART) vs ART alone in the treatment of HIV in patients with CD4 cell counts ≥ 300 cells/mm³. The mean decreases in average HCV RNA levels (copies/mL, log (10)) were 0.28 log in the IL-2 group (n = 26) and 0.04 log in the ART alone group (n = 28) at 12 months (P = 0.18). The changes in HCV RNA level were not associated with baseline or nadir CD4 cell counts, baseline aspartate aminotransferase, CD4 cell response to IL-2, or changes in plasma HIV RNA values. Compared with those participants who only had HIV, the HIV/HCV co-infected patients did not have a significantly different CD4 cell response to IL-2 therapy. Intermittent IL-2 therapy does not produce a significant sustained decrease in plasma HCV RNA levels among patients co-infected with HIV/HCV who are on highly active ART.

Tedaldi E, Huppler Hullsiek K, Malvestutto C, Arduino R, Fisher E, Gaglio P, Jenny-Avital E, McGowan J, Perez G. Prevalence and characteristics of HCV coinfection in an HIV clinical trials group. *Clin Infect Dis* 2003 May 15;36(10):1313-7. Epub 2003.

The baseline prevalence of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) coinfection among 2705 patients enrolled in HIV clinical trials in the Community Programs for Clinical Research on AIDS (CPCRA) was 16.6%. For men, multivariate logistic regression showed that the baseline prevalence of HIV-HCV coinfection was positively associated with history of injection drug use, older age, antiretroviral therapy naive status, African American or Latino ethnicity, and no history of having sex with men. No association was found with baseline CD4+ cell count or HIV RNA level. The prevalence of HCV coinfection in a diverse HIV clinical trials cohort provides additional information about risk behaviors and demographic factors that can be used in the analysis of clinical and virologic outcomes.

Shlay JC, El-Sadr WM, Bartsch G, Wang J, Gibert C, Carr A, Raghavan SS. A simple questionnaire to assess alterations in body appearance in HIV-infected patients. *Int J Body Composition Research* 2003;1(2):81-90.

This questionnaire was developed in order to assess perception of any changes in body appearance and to determine its potential use in a large diverse cohort of antiretroviral naive HIV-infected patients. For this study, HIV-infected patients (n=227) enrolling into a metabolic study completed a ten-item questionnaire on alterations in body appearance and had body mass index (BMI) and anthropometric measurements performed. The questionnaire assessed subjective changes in body appearance over the past four months (thinning, no change, increase in sizes). Concordance of survey results with mean body circumference (arm, waist, hip, thigh), mean skinfold thickness (triceps, suprascapular, subscapular, abdomen, thigh) and the BMI were evaluated. At baseline, over a third of participants reported no changes for all six sites (i.e., face, arms, breast, waist, buttocks, thighs); however, of those reporting any changes for all six sites, thinning was more common (7.9%) than was an increase in sizes (0.4%). For the body circumference, perceived changes of face, breast, waist, buttocks, and thighs were positively correlated with the mean values for all measure body circumferences ($P \leq 0.18$). For the skinfolds, changes in face, buttocks, waist and thighs were positively correlated with all five skinfold thickness measurements ($P < 0.05$); arms and breast were positively correlated with all measurements except suprascapular (arms: $P=0.06$, abdomen (arms: $P=0.13$, breast: $P=0.12$) and triceps (breast: $P=0.21$). For face, arms, waist, buttocks and thighs, self-reported body perception was correlated with mean BMI ($P < 0.05$). In conclusion, responses from the survey correlated well with body circumference and skinfold measurements, supporting the potential use of this simple questionnaire in antiretroviral naive adults.

Reisler RB, Han C, Burman WJ, Tedaldi EM, Neaton JD. Grade 4 events are as important as AIDS events in the era of HAART. *J Acquir Immune Defic Syndr Hum Retrovirol* 2003;34:379-386.

Objective: To estimate incidence and predictors of serious or life-threatening events that are not AIDS defining, AIDS events, and death among patients treated with highly active antiretroviral therapy (HAART) in the setting of 5 large multicenter randomized treatment trials conducted in the United States. **Methods:** Data were analyzed from 2947 patients enrolled from December 1996 through December 2001. All patients were to receive antiretrovirals throughout follow-up. Data collection was uniform for all main outcome measures: serious of life-threatening (grade 4) events, AIDS, and death. **Results:** During follow-up, 675 patients experienced a grade 4 event (11.4 per 100 person-years); 332 developed an AIDS event (5.6 per 100 person-years); and 272 died (4.6 per 100 person-years). The most common grade 4 events were liver related (148 patients, 2.6 per 100 person-years). Cardiovascular events were associated with the greatest risk of death (hazard ratio = 8/64; 95% CI: 5.1 to 14.5). The first grade 4

CPCRA Cross-Protocol Articles, cont.

event and the first AIDS event were associated with similar risks of death, 5.68 and 6.95, respectively. **Conclusions:** Grade 4 events are as important as AIDS events in the era of HAART. To adequately evaluate the impact of HAART on morbidity, comorbidities and other key factors must be carefully assessed.

Mannheimer S, Friedland G, Matts J, Child C, Chesney M. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clin Infect Dis* 2002; 34:1115-1121.

We prospectively studied long-term antiretroviral adherence patterns and their impact on biologic outcomes for human immunodeficiency virus (HIV)-infected participants in 2 randomized, multicenter clinical trials. For the period from baseline to month 12 of the study, participants who reported adherence levels of 100%, 80%-99%, and 0%-79% had plasma HIV RNA levels that decreased by 2.77, 2.33, and 0.67 log₁₀ copies/mL, respectively (P <.001), whereas their CD4 counts increased by 179, 159, and 53 cells/mm³, respectively (P <.001). Adherence predicted nondetectable HIV RNA levels (<50 copies/mL) at 12 months of follow-up (P <.01). The HIV RNA level was nondetectable on 72% of participants who reported 100% adherence at all 4 follow-up visits,

compared with 66%, 41%, 35%, and 13% of participants who reported 100% adherence at 3, 2, 1, or 0 follow-up visits, respectively (P <.001). Onwhite race was associated with poorer adherence (P <.001), and older age was associated with better adherence (P <.001).

Wheeler DA, Gibert CL, Launer CA, Muurahainen N, Elion RA, Abrams DI, et al. Weight loss as a Predictor of survival and disease progression in HIV infection. *J Acquir Immune Defic Syndr Hum Retrovirol*1998;18(1)80-85.

Severe weight loss in HIV is associated with decreased survival. A loss of less than five percent of body weight over four months is associated with an increased risk of death and opportunistic complication in HIV. More than five percent weight loss is associated with an increased risk of individual opportunistic complications.

Saravolatz L, Neaton JD, Sacks L, Deyton L, Rhame F, Sherer R. CD4+ T lymphocyte counts and patterns of mortality among patients infected with the human immunodeficiency virus who were enrolled in the Community Programs for Clinical Research on AIDS. *Clin Infect Dis* 1996;22(3):513-520.

CD4+ T lymphocyte measurements are used frequently in clinical practice and have important prognostic implications. In each CD4+ cell stratum, mortality rates were higher for those with a history of disease progression at entry into the study; across all CD4+ cell strata, mortality was 60% greater. These data should be useful in planning clinical trials, and they have implications in terms of the frequency with which CD4+ cell counts should be measured to monitor the progression of HIV infection.

Chan ISF, Neaton JD, Saravolatz LD, Crane LR, Osterberger J. Frequencies of opportunistic diseases prior to death among HIV infected persons. *AIDS* 1995;9:1145-1151.

The investigators report on the results of a descriptive case series study, designed to provide a history of opportunistic events experience by 1,205 HIV-infected CPCRA patients before their deaths and to determine whether the frequency of events varies according to demographic characteristics, risk behaviors, or geographic location. PCP, MAC, CMV, wasting syndrome, invasive candidiasis, and bacterial pneumonia are the most common opportunistic AIDS-defining events experienced by these patients prior to death. Continued research on the etiology and prevention of these diseases should be a high priority.

Melnick SL, Sherer R, Louis TA, Hillman D, Rodriguez EM, Lackman C, et al. Survival and disease progression according to gender of patients with HIV infection. *JAMA* 1994;272(24):1915-1921.

This multicenter cohort study was designed to compare disease progression and mortality between women (n=768) and men (n=3779) infected with HIV, while controlling for differences in baseline predictors of disease progression. The study showed that women were at higher risk for death and bacterial pneumonia than men but that risk for disease progression was not significantly different between genders. The survival difference might be attributed to differential access to or utilization of health care resources, including antiretroviral therapy and PCP prophylaxes. Other reasons for lower survival in women might include differences in HIV-infected men and women with respect to socioeconomic status, homelessness, domestic violence, substance

abuse, and degree of social support. The authors identified the relative impact of diverse social factors on survival as an area which requires further study. They also mentioned the importance of accurate information on causes of death in this type of research and

CPCRA Cross-Protocol Articles, cont.

discuss the limitations of their data on causes of death. An important clinical finding regarding the natural history of HIV infection was the lack of a difference in the incidence of, and morbidity and mortality from, HIV-related conditions, including the common AIDS-defining opportunistic infections and malignancies. The implication for clinicians who care for HIV-infected women is that treatment choices, drug dosages, and clinical outcomes from studies conducted exclusively or primarily on men may reasonably be applied to the care of HIV-infected women. At the same time, clinicians need to be more attentive to features of HIV infection in women which may be associated with increased mortality and morbidity in women, such as domestic violence and chemical dependency.

CPCRA Protocol Collaborations

Data Collection of Adverse Events of Anti-HIV Drugs (D:A:D) Study

Weber R, Sabin CA, Friis-Møller N, Reiss P, El-Sadr WM, Kirk O, Dabis F, Law MG, Pradier C, De Wit S, Åkerlund B, Calvo G, d'Arminio Monforte A, Rickenbach M, Ledergerber, Phillips AN, Lundgren JD. Liver-related deaths in persons infected with the human immunodeficiency virus. *Arch Intern Med* 2006;166:1632-1641.

Background: An increasing proportion of deaths among human immunodeficiency virus (HIV)-infected persons with access to combination antiretroviral therapy (cART) are due to complications of liver diseases. **Methods:** We investigated the frequency of and risk factors associated with liver-related deaths in the Data Collection on Adverse Events of Anti-HIV Drugs study, which prospectively evaluated 76,893 person-years of follow-up in 23,441 HIV-infected persons. Multivariable Poisson regression analyses identified factors associated with liver-related, AIDS-related, and other causes of death. **Results:** There were 1,256 deaths (5.3%; 1.6 per 100 person-years); 14.5% were from liver-related causes. Of these, 16.9% had active hepatitis B virus (HBV), 66.1% had hepatitis C virus (HCV), and 7.1% had dual viral hepatitis co-infections. Predictors of liver-related deaths were latest CD4 cell count (adjusted relative rate [RR], 16.1; 95% confidence interval [CI], 8.1-31.7 for <50 vs $\geq 500/\mu\text{L}$), age (RR, 1.3; 95% CI, 1.2-1.4 per 5 years older), intravenous drug use (RR, 2.0; 95% CI, 1.2-3.4), HCV infection (RR, 6.7; 95% CI, 4.0-11.2), and active HBV infection (RR, 3.7; 95% CI, 2.4-5.9). Univariable analyses showed no relationship between cumulative years patients were receiving cART and liver-related death (RR, 1.00; 95% CI, 0.93-1.07). Adjustment for the most recent CD4 cell count and patient characteristics resulted in an increased risk of liver-related mortality per year of mono or dual antiretroviral therapy before cART (RR, 1.09; 95% CI, 1.02-1.16; $P=0.008$) and per year of cART (RR, 1.11; 95% CI, 1.01-1.21; $P=0.02$). **Conclusions:** Liver-related death was the most frequent cause of non-AIDS-related death. We found a strong association between immunodeficiency and risk of liver-related death. Longer follow-up is required to investigate whether clinically significant treatment-associated liver-related mortality will develop.

Thiébaud R, El-Sadr WM, Friis-Møller N, Rickenbach M, Reiss P, D'Arminio Monforte A, Morfeldt L, Fontas E, Kirk O, De Wit S, Calvo G, Law MG, Dabis F, Sabin CA, Lundgren JD for the "Data Collection of Adverse Events of Anti-HIV Drugs" (D:A:D) Study Group. Predictors of hypertension and changes of blood pressure in HIV-infected patients. *Antivir Ther* 2005;10:811-823.

Objective: We assessed predictors of changes in systolic (SBP) and diastolic (DBP) blood pressure during follow-up and of the development of hypertension in HIV-infected individuals. **Methods:** International cohort collaborative study (D:A:D) of established prospective cohorts of HIV-1-infected patients. Longitudinal analysis of changes in blood pressure (BP) was performed using mixed effects models in 17170 patients. Predictors of development of hypertension during follow-up (systolic BP ≥ 140 and/or diastolic BP ≥ 90 mmHg or initiation of antihypertensive treatment) were assessed using Cox models in 8984 patients with a normal BP level at baseline. **Results:** 73548 BP measurements with a median of 4 per patient (interquartile range [IQR]: 2-6) were recorded over a median follow-up of 2.3 years (IQR: 1.5-2.6). Risk factors significantly associated with a development of higher systolic CP and diastolic CP (differenced ≥ 5 mmHg and P -values <0.001) during follow-up were: older age, male sex, higher body mass index (BMI) and use of BP-lowering drugs. In patients with normal BP at baseline, 1186 develop hypertension for an incidence of 72.1 per 1000 person-years (95% confidence interval : 68.2-76.0). Factors associated with development of hypertension were: male sex, higher BMI, older age, higher CP at baseline, high total cholesterol and clinical lipodystrophy. Cumulative duration of exposure to nucleoside reverse transcriptase inhibitors ($P=0.75$), protease inhibitors ($P=0.92$) as well as type of antiretroviral treatment at baseline ($P=0.18$) were not associated with a higher risk of hypertension. Cumulative duration of exposure to non-nucleoside reverse transcriptase inhibitors (NNRTIs) was significantly associated with lower risk of hypertension (hazard ratio=0.78 and 0.67 for those treated ≤ 10 months and >10 months compared with no exposure; $P=0.005$). **Conclusions:** Increased blood pressure in HIV-infected individuals is associated with established risk factors for hypertension. There was no evidence for an independent deleterious effect of any class of antiretroviral drugs on BP, although the use of NNRTIs was associated with a lower risk of development of hypertension.

d'Armino Monforte A, Sabin CA, Reiss P, Weber R, Kirk O, El-Sadr W, De Wit S, Mateu S, Petoumenos K, Davis F, Pradier C, Morfeldt L, Phillips AN, Lundgren JD, Friis-Møller N, for the D:A:D Study Group. Cardio- and cerebrovascular events in HIV-infected persons. *AIDS* May 21, 2004;18:1811-1817.

Objective: Recent results from the D:A:D Study indicated that the incidence of myocardial infarction (MI) increased by 26% per year of exposure to combination antiretroviral treatment (cART). The present study was performed to investigate whether this risk was similar when including other cardio- and cerebro-vascular disease events (CCVE). **Design:** D:A:D is an international collaboration of 11 cohorts, following 23,468 HIV-infected patients prospectively at 188 clinics in 21 countries situated in Europe,

CPCRA Protocol Collaborations, cont.

Data Collection of Adverse Events of Anti-HIV Drugs (D:A:D) Study, cont.

USA and Australia. **Methods:** The end-point was the occurrence of a first CCVE during prospective follow-up, defined as the first of: acute MI, invasive cardiovascular procedures, stroke, or death from other cardiovascular disease. Relative rates (RR) for CCVE from Poisson regression models and 95% confidence intervals (VI) are reported. All models are adjusted for other risk factors for CCVE, including age, gender, ethnicity, family history, body mass index, and smoking status as well as cohort and HIV transmission group. **Results:** Over 36,145 person-years of follow-up, 207 patients experienced at least one CCVE (23.7% fatal). The first event was MI in 127 patients, invasive cardiovascular procedure in 39 patients, stroke in 38 patients, and death from other cardiovascular disease in four patients. The incidence of first CCVE was 5.7 per 1000 person-years [95% confidence interval (CI) 5.0-6.5] and increased with longer exposure to CART (RR per year of exposure, 1.26; 95% CI, 1.14-1.38; P <0.0001). **Conclusion:** CART increases the risk of CCVD, and this increase is comparable with how CART affects the risk of MI. This finding is consistent with the hypothesis that atherosclerosis is a side-effect of CART.

Fontas E, van Leth F, Sabin CA, Friis-Møller N, Rickenbach M, d'Arminio Monforte A, Kirk O, Dupon M, Morfeldt L, Mateu S, Petoumenos K, El-Sadr W, de Wit S, Lundgren JD, Pradier C, Reiss, P, for the D:A:D Study Group. Lipid Profiles in HIV-Infected Patients Receiving Combination Antiretroviral Therapy: Are Different Antiretroviral Drugs Associated with Different Lipid Profiles? *J Infect Dis* March 15, 2004;189:1056-74.

Levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c), as well as the TC:HDL-c ratio, were compared in patients receiving different antiretroviral therapy regimens. Patients receiving first-line regimens including protease inhibitors (PIs) had higher TC and TG levels and TC:HDL-c ratios than did antiretroviral-naïve patients; patients receiving 2 PIs had higher levels of each lipid. Ritonavir-containing regimens were associated with higher TC and TG levels and TC:HDL-c ratios than were indinavir-containing regimens; however, receipt of nelfinavir was associated with reduced risk of lower HDL-c levels, and receipt of saquinavir was associated with lower TC:HDL-c ratios. Patients receiving non-nucleoside reverse-transcriptase inhibitors had higher levels of TC and LDL-c than did antiretroviral-naïve patients, although the risk of having lower HDL-c levels was lower than that in patients receiving a single PI. Efavirenz was associated with higher levels of TC and TG than was nevirapine.

Friis-Møller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, Thiebaut R, Morfeldt L, De Wit S, Pradier C, Calvo G, Law MG, Kirk O, Phillips AN, Lundgren JD. Combination Antiretroviral Therapy and the Risk of Myocardial Infarction. *N Engl J Med* November 20, 2003;349:1993-2003.

Background: It remains controversial whether exposure to combination antiretroviral treatment increases the risk of myocardial infarction. **Methods:** In this prospective observational study, we enrolled 23,468 patients from 11 previously established cohorts from December 1999 to April 2001 and collected follow-up data until February 2002. Data were collected on infection with the human immunodeficiency virus and on risk factors for and the incidence of myocardial infarction. Relative rates were calculated with Poisson regression models. Combination antiretroviral therapy was defined as any combination regimen of antiretroviral drugs that included a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor. **Results:** Over a period of 36,199 person-years, 126 patients had a myocardial infarction. The incidence of myocardial infarction increased with longer exposure to combination antiretroviral therapy (adjusted relative rate per year of exposure, 1.26 [95 percent confidence interval, 1.12 to 1.41]; P <0.001). Other factors significantly associated with myocardial infarction were older age, current or former smoking, previous cardiovascular disease, and male sex, but not a family history of coronary heart disease. A higher total serum cholesterol level, a higher triglyceride level, and the presence of diabetes were also associated with an increased incidence of myocardial infarction. **Conclusions:** Combination antiretroviral therapy was independently associated with a 26 percent relative increase in the rate of myocardial infarction per year of exposure during the first four to six years of use. However, the absolute risk of myocardial infarction was low and must be balanced against the marked benefits from antiretroviral treatment.

CPCRA Protocol Collaborations, cont.

Data Collection of Adverse Events of Anti-HIV Drugs (D:A:D) Study, cont.

Friis-Moller N, Weber R, Reiss P, Thiebaut R, Kirk O, d'Arminio Monforte A, et al for the DAD study group. Results from the DAD study: Cardiovascular disease risk factors in HIV patients - association with antiretroviral therapy. *AIDS* May 23, 2003; 17(8):1179-1193.

The purpose of the D.A.D. Study is to determine the prevalence of risk factors for cardiovascular disease (CVD) among HIV-infected persons, to investigate any association between such risk factors, stage of HIV disease, and use of antiretroviral therapies, and to follow patients for the possible development of cardiovascular events. The initial study results which reports the baseline information about these patients being followed for the next few years were reported at the Retrovirus Conference in Feb 2003 and now an official publication current issue of the journal AIDS. This initial look at the patients and potential risk factors includes examining levels of cholesterol, triglycerides, diabetes, hypertension, the types of HAART regimens patients are taking, and body changes & their association with lipid abnormalities.

CPCRA Methodological/Ancillary Articles

Rouff J, Child C. Application of quality improvement theory and process in a national multicenter HIV/AIDS clinical trials network. *Qual Manag Health Care* 2003;12(2):89-96.

Effective clinical trials depend on the production of scientifically sound data. Clinical research coordinators monitor various activities to assure that data meet standards for timeliness and quality. Traditional methods of assuring data quality are less than optimal because they are based on correcting mistakes after they occur. Because they are focused on problem prevention, the techniques of continuous quality improvement represent a more effective means of maintaining high quality of data. This article describes the means by which principles of continuous quality improvement were incorporated into an HIV/AIDS clinical research network, as well as outcomes associated with these efforts.

Han C, Pulling CC, Telke SE, Huppler Hullsiek K. Assessing the utility of five domains in SF-12 health Status questionnaire in an AIDS clinical trial. *AIDS* 2002; 16:431-439.

Objective: To assess a shortened quality-of-life (QoL) measurement tool in a population with advanced HIV infection. **Conclusions:** For the domains considered, SF-12 is a reasonable and effective replacement for SF-39 in studies of patients with advanced HIV disease. SF-12 reduces item redundancy and the burden of data requirements for both investigators and patients; consequently, it may improve compliance with form completion.

Tsai C, Chaloner K. Using prior opinions to examine sample size in a clinical trial: two examples. In: *Case Studies in Bayesian Statistics*, Kass RE et al, eds. New York: Springer-Verlag; 2001:409-423.

Chaloner K, Rhame FS. Quantifying and documenting prior beliefs in clinical trials. *Stat Med* 2001; 20:581-600.

Collecting and documenting subjective prior beliefs from knowledgeable clinicians about the potential results of a clinical trial has many advantages. Two large trials or prophylactic treatments in an HIV-positive population are used as examples. The trials recruited patients of primary care physicians and compared treatments which were in use in clinical practice. Opinions about these trials were elicited from 58 practising HIV clinicians. It is shown how the documented opinions can be used by the monitoring board to anticipate the clinicians' reaction to the results. Eliciting prior beliefs is also ethically important for documenting the nature of the uncertainty or equipoise. Important information is provided for the informed consent process and Institutional Review Board (IRB).

Eberly LE, Ohman PA, Neaton, JD, Price RW, Abrams DI. Kaposi's Sarcoma and central nervous system disease: a real association or an artifact of the control group? *AIDS* 2000; 14:995-1000.

This was an observational study to test the hypothesis that Kaposi's sarcoma (KS) protects against four central nervous system (CNS) diseases in HIV-1-infected individuals. The study population of 9,404 subjects included participants from CPCRA protocols. The analyses indicate that the risk of CNS disease associated with Kaposi's sarcoma depends strongly on the reference or control group chosen. When compared to individuals with other non-KS AIDS-defining diseases, Kaposi's sarcoma is associated with a lower risk of CNS disease in HIV-1 positive individuals. However, when compared to individuals with no AIDS-defining disease or with a similarly mild AIDS-defining disease such as invasive candidiasis, Kaposi's sarcoma is associated with an equivalent risk of CNS disease.

Johnson B, Carlin B, Hodges JS. Cross-study hierarchical modeling of stratified clinical trial data. *J BiopharmStat* 1999;9(4):617-640.

Hierarchical random-effects models can be used to estimate treatment or other covariate effects in single-study analyses coordinated over multiple clinical units and can also be extended to a wide variety of cross-study applications. After reviewing the single-case study, we use data from five trial protocols to look for units that tend to have treatment effects consistently above or below the study-specific grand mean across several studies. As a first step, we summarize the patient-level data as study-specific and unit-specific estimated treatment effects and standard errors using independent Cox regression models. We then compare the results of a hierarchical model using these data summaries as input to those produced by a more fully Bayesian method that uses the actual patient-level survival data. We also compare various different models using a deviance information criterion, a recent extension of the Akaike information criterion designed for hierarchical models. Our procedure appears to be effective at answering the question whether certain clinical units of the Terry Bein Community Programs for Clinical Research on AIDS are better than others at identifying treatment effects where they exist.

CPCRA Methodological/Ancillary Articles, cont.

Cox LE, Rouff JR, Svendsen KH, Markowitz M, Abrams DI. Community advisory boards: Their role in AIDS clinical trials. *Health Soc Work* 1998;23(4)290-297.

Community-based AIDS research programs were initially federally funded in 1989. Since then the Terry Bein Community Programs for Clinical Research on AIDS has mandated that research units develop and maintain community advisory boards to provide advice and communicate community preferences in AIDS research. Seventeen community-based AIDS research units formed community advisory boards (CABs) based on a model developed by the Community Consortium at San Francisco General Hospital. Social workers employed by these AIDS research units surveyed 267 CAB members to ascertain board characteristics and members' perceptions of program activities. Implication for social work and future research are discussed.

Green LA, Rhame FS, Price RW, Perlman DC, Capps LG, Sampson J, et al. Experience with a cross-study endpoint review committee for AIDS clinical trials. *AIDS* 1998;12:1983-1990.

This paper describes the methods and results of a standardized system for clinical endpoint determination for defining and reviewing endpoints in clinical trials for HIV-infected individuals. Uniform classification of endpoints across AIDS clinical trials can be accomplished by multicenter, multitrial organizations with standardized definitions and review of endpoint documentation. Our experience suggests that nurse coordinators reviewing all submitted endpoints for every trial are warranted and the need for external review by a clinical events committee may depend on the type of trial conducted.

Matts JP, Launer CA, Nelson ET, Miller C, Dain B. A graphical assessment of the potential impact of losses to follow-up on the validity of study results. *Stat Med* 1997;16:1943-1954.

Losses to follow-up in clinical trials -- patients for whom it is unknown if the outcome of interest has occurred -- can bias study results. If we investigate extreme case scenarios and find the study results do not change much, impact is negligible. If not, we may need to interpret the study's results with caution. At issue is how much caution do we need? We describe a graphical approach to assess the potential impact of losses to follow-up on the validity of study results. One can create the graphs using design estimates and interim or final data. We give two examples using design parameters and another example modeled after observed data from clinical trials conducted by the CPCRA. The examples illustrate that tolerable levels of losses to follow-up change depending on the overall outcome and direction of differential losses.

Larntz K, Neaton JD, Wentworth DN, Yurik T. Data analysis issues for protocols with overlapping enrollment. *Stat Med* 1996;15:2445-2453.

Many persons with HIV require and take several medications. The efficacy and safety of many of these medications are uncertain. Approaches to data analysis, based on intention-to-treat, for individual and pairs of trials are described. An antiretroviral trial and a trial for prophylaxis of *Pneumocystis carinii* pneumonia (PCP) are used for illustration. The authors concluded that such analyses may yield useful information on drug interactions and that a more vigorous coenrollment policy should be pursued in AIDS research.

Carlin BP. In: Gilks WR, Richardson S, Spiegelhalter DJ editors. Hierarchical longitudinal modeling. Markov Chain Monte Carlo in Practice. London: Chapman & Hall; 1996. p. 303-319.

Bayesian models of virtually unlimited complexity may now be seriously contemplated. Since most practicing statisticians learned the art of data analysis prior to the MCMC Bayesian revolution, most should probably receive a certain amount of retraining in order to avoid these pitfalls and take full advantage of this exciting new methodology. In the case of models for longitudinal data, several guidelines are given.

Bjorling LE, Hodges JS. Rule-based ranking schemes for antiretroviral trials. *Stat Med* 1996;16:1175-1191.

Often a trial's outcome measure is straightforward but not in trials of treatments for HIV infection. Currently, the nearly universal choice for a clinical outcome is the first occurrence or recurrence of an AIDS-defining condition or death. This paper discusses difficulties with this outcome measure and considers alternatives to it. This discussion leads to a consideration of rule-based ranking schemes that use more information than does first disease progression.

CPCRA Methodological/Ancillary Articles, cont.

Shih JH, Louis TA. Inferences on the association parameter in copula models for bivariate survival data. *Biometrics* 1995;51:1384-1399.

A two-stage parametric and a two-stage semi-parametric estimation procedures for the association parameter in copula models are investigated. For the two-stage parametric estimation procedure, the estimate of the association parameter is efficient and the parameter estimates in the margins have high efficiency and are robust to misspecification of dependency structures. For the two-stage semi-parametric estimation, the estimate of the association parameter is efficient at independence. Proposed methods to an AIDS data set for illustration are applied.

Neaton JD, Wentworth DN. Considerations in specifying the duration of followup of antiretroviral trials. *Med Biol Environ* 1995;23(2):171-179.

This paper asserts that the duration of followup of antiretroviral trials should be longer and that research questions should be formulated as strategy questions with nested studies of specific agents of combination of agents. This approach has the potential for both quantifying the relative short-term efficacy of specific drugs or combinations and providing data to develop better practice guidelines for using antiretrovirals over long time periods.

Morse EV, Simon PM, Besch CL, Walker J. Issues of recruitment, retention, and compliance in community-based clinical trials with traditionally underserved populations. *Applied Nurs Res* 1995; 8(1):8-14.

The investigators present data from a prospective study of potential barriers to enrollment and retention conducted during startup of 14 CPCRA units. The study had the additional purpose of delineating and evaluating the efficacy of various strategies used by the CPCRA clinical staff to reduce barriers to recruitment and retention. The study found that the success of the unit, in terms of its ability to accrue patients, may be dependent on its awareness of barriers and its ability to implement clinic-based strategies to enhance recruitment, retention, and compliance.

Korzun A, Chaloner K. Protocol development. In: Finkelstein DM and Schoenfeld DA editors. *AIDS Clinical Trials*. Wiley-Liss, Inc., New York; 1995. p. 67-89.

Besch CL. Compliance in clinical trials. *AIDS* 1995;9:1-10.

The author, in this editorial review, provides an overview of the types of compliance important positive and negative influencing factors, methods of measurement, and strategies that can improve compliance. The importance of compliance has been recognized in HIV research and care. Suggestions for future research with respect to HIV care include (1) identification of useful models of behavioral response that can predict or anticipate compliance with preventive and therapeutic treatments in the patient groups most impacted, (2) identification and description of cultural influences on medical care and response to health recommendations, and (3) development of specific interventions for the medically underserved populations affected by the HIV epidemic.

Neaton JD, Wentworth DN, Rhame F, Hogan C, Abrams DI, Deyton L. Methods of studying interventions: Considerations in choice of a clinical endpoint for AIDS clinical trials. *Stat Med* 1994;13:2107-2125.

In most clinical trials of antiretroviral therapy for patients infected with HIV, the major outcome variable has been the combined clinical endpoint of any new or recurrent AIDS- defining event. The authors review features of combined endpoints and used data from the Terry Bein Community Programs for Clinical Research on AIDS (CPCRA) to evaluate this outcome measure in terms of relevance, diagnostic certainty, and sensitivity. They conclude that the combined endpoint is not relevant because (1) the 19 different events constituting the combined endpoint are equally weighted in analyses even though they vary considerably in terms of risk of death and (2) the events after the first are ignored, and, thus, the event profile of patients is not taken into account in making treatment comparisons. The authors recommend that survival be the primary endpoint of antiretroviral trials and that all opportunistic events experienced by patients, not just the first, be collected and summarized.

CPCRA Methodological/Ancillary Articles, cont.

Carlin BP, Chaloner KM, Louis TA, Rhame FS. Elicitation, monitoring, and analysis for an AIDS clinical trial. In: Gatsonis C, Hodges JS, Kass RE, and Singpurwalla ND editors. Case Studies in Bayesian Statistics. New York: Springer-Verlag; 1994 2:48-49.

Bayesian methods have been a subject of increasing interest among researchers engaged in the interim monitoring and final analysis of clinical trials data. In this paper the practical application of Bayesian methodology to the analysis of clinical trial data, with emphasis on issues particularly relevant for AIDS trials is discussed. The performance of this methodology when applied to a trial conducted by the CPCRA is reported. The results indicate which phases of the analysis are well handled using currently available techniques, and which phases seem to require further methodological development. Potential solutions to some of these problem areas and discussed and the nature of the research questions for some of those that remain are described.

Chaloner K, Church T, Louis TA, Matts JP. Graphical elicitation of a prior distribution for a clinical trial. *The Statistician* 1993;42:341-353.

Bayesian methods are potentially useful for the design, monitoring and analysis of clinical trials. This paper describes a method to help quantify beliefs in the form of a prior distribution about regression coefficients in a proportional hazards regression model. The method was developed for, and is applied to, a randomized trial comparing prophylaxes for toxoplasmosis in a population of HIV-positive individuals. Prior distribution from five AIDS experts are elicited.

Carlin BP, Chaloner K, Church T, Louis TA, Matts JP. Bayesian Approaches for monitoring clinical trials with an application to toxoplasmic encephalitis prophylaxis. *The Statistician* 1993;42(4):355-367.

Bayesian methods have been a subject of increasing interest among researchers engaged in the interim monitoring and final analysis of clinical trials data. Computational issues are investigated by comparing the posterior distributions of model parameters obtained assuming approximate posterior normality with more precise results obtained via numerical integration. The impact of approximations on the performance of Bayesian stopping rules was also investigated. Where the normal approximation is inappropriate, the Bayesian methodology still allows for inference and simple monitoring displays based on posterior probabilities. The methodology with a numerical example featuring prior distributions elicited from five AIDS experts and data from a recently completed toxoplasmic encephalitis prophylaxis trials are illustrated.

El-Sadr W, Capps L. The challenge of minority recruitment in clinical trials for AIDS. *JAMA* 1992;267(7):954-957.

There are significant obstacles to the participation of minorities in clinical trials. The problem of basing medical recommendations for the entire HIV-infected population on results of clinical trials in which minorities are not adequately represented is that the results may not apply to them and women. The authors suggests that the compelling scientific, ethical, and social reasons for inclusion of minorities in clinical trials justify the necessary efforts to accomplish this goal. The CPCRA program is an attempt to increase minority recruitment in HIV disease clinical trials.