Safety and Efficacy of Solid Organ Transplantation in HIV-Positive Patients

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THE SUCCESS OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) can easily be gauged by the fact that fewer patients are dying of AIDS-related manifestations than ever before. However, there has been a relatively sharp increase in the number of deaths from other complications, including end-stage organ disease. Two articles published in this issue of *The PRN Notebook* outline the growing reality of severe liver disease among HIV-positive patients with chronic hepatitis B and hepatitis C infections. There are also a growing number of reports of renal disease in HIV, including HIV-associated nephropathy, and people with HIV infection are vulnerable to all the other common causes of end-stage renal disease including glomerulonephritis, IgA nephropathy, amyloid, and diabetes mellitus.

For patients with end-stage liver and kidney disease—not to mention patients with end-stage lung and heart disease—transplantation may be the only option. According to the American Council on Transplantation, more than 50,000 people benefit from organ transplantation every year. The United Network for Organ Sharing (UNOS) concurs and has always allowed HIV-positive patients to add their names to its organ waiting list (UNOS still excludes potential donors known to be HIV-positive or perceived to be carriers of the virus [e.g., gay men, intravenous drug users, prostitutes]). However, many insurance companies and transplant centers balk at the idea of transplantation involving HIV-positive patients based on two factors.

First, before the advent of HAART, people with HIV infection had a shortened lifespan as a result of immune deficiency and the risk of life-threatening complications. Compounded by the facts that donors are rare and demand is high, transplant centers often consider projected survival in deciding who receives a coveted organ. A second concern has been that major surgery and the use of immunosuppressive drugs to prevent organ rejection may exacerbate an HIV-positive patient's immune deficiency, causing rapid disease progression and death.

Right off the bat, it's safe to say that HAART has significantly altered the natural history of HIV infection and that the projected lifespan of HIV-infected patients is, perhaps, on a par with that of other patients with chronic illnesses such as diabetes and hypertension. Thus, it can be strongly argued that exclusion of HIV-positive patients from transplantation based solely on the fear of shortened survival no longer holds water. What remain, however, are concerns regarding the efficacy of organ transplantation and the safety of immunosuppressive drugs in HIV-infected patients.

Drs. Michelle Roland, Peter Stock, and their colleagues at the University of California San Francisco (UCSF) recently received a substantial $2 million in State of California funding to evaluate transplant safety in a small number of HIV-positive people with end-stage kidney and liver disease. At the November 2000 meeting of PRN, Dr. Roland provided a litany of data regarding organ transplantation in the setting of HIV and introduced members to the groundbreaking and incredibly ambitious UCSF study now under way, along with the multisite study currently under development.

Attitudes Toward Transplantation And Historical Experience

TO EXPLORE THE ATTITUDES OF U.S. TRANSplant centers toward kidney transplants in HIV-infected patients with end-stage renal disease, Dr. Aaron Spital of the University of Rochester School of Medicine mailed a survey to 248 renal transplant centers in the United States (Spital, 1998). All 149 of the 248 (60%) responding centers said they require HIV testing of prospective kidney recipients, and 84% of these centers would not accept an individual who refused HIV testing. The vast majority of responding centers would not transplant a kidney from a cadaveric (88%) or a living donor (91%) into an asymptomatic HIV-infected patient who is otherwise a good candidate for transplantation. Among the few centers that would consider transplanting an HIV-infected patient, not a single center had performed such a transplant in the year prior to the survey. Most centers feared that transplantation in the face of HIV infection would be harmful to the individual, and some believed that it would be a waste of precious organs.

As pessimistic as Dr. Spital's findings seem, Dr. Roland seemed much more positive. "We have 14 transplant centers throughout the United States who are enthusiastic about our transplant study at UCSF and are actively participating in the development of a multisite study, some of which are already performing such transplants. This really impressed us and I think it reflects a growing trend among surgeons and transplant centers. It's a matter of education, really. Transplant surgeons who are familiar with the progress made in recent years or who work with HIV specialists are much more open-minded. This interest in the transplant world is growing in leaps and bounds."

The greatest amount of experience with organ transplantation in HIV-infected people was in the pre-HAART era. While some of the initial reports demonstrated worse outcomes following transplantation in these patients, other reports have suggested that HIV-infection does not have adverse effects on graft survival.

Table 1. Adult Graft and Patient Survival Rates for Liver and Kidney Transplants: UNOS National Results

		One-month survival for transplants performed 1/1/97-12/31/98 with follow-up through 1/31/99.	One-year survival for transplants performed 1/1/97-12/31/98 with follow-up through 12/31/99.	Three-year survival for transplants performed 1/1/95-12/31/96 with follow-up through 12/31/99.
LIVER TRANSPLANTS				
GRAFT	**Number of transplants**	**7,161**	**7,161**	**6,724**
	Follow-up (%)	96.0	91.7	92.8
	Survival (%)	90.0	79.8	68.8
PATIENT	**Number of patients**	**6,755**	**6755**	**6,283**
	Follow-up (%)	95.8	90.9	92.0
	Survival (%)	94.0	85.6	75.9
KIDNEY TRANSPLANTS				
GRAFT	**Number of transplants**	**22,423**	**22,423**	**20,791**
	Follow-up (%)	94.3	88.7	91.3
	Survival (%)	96.1	90.5	79.4
PATIENT	**Number of patients**	**22,341**	**22,341**	**20,682**
	Follow-up (%)	93.7	86.8	87.9
	Survival (%)	99.0	95.6	90.5

Nationwide cadaveric-graft survival and patient survival rates reported by the United Network for Organ Sharing (UNOS), based on data collected by the National Organ Procurement and Transplantation Network (OPTN) and the Scientific Registry of Transplant Recipients. HIV-specific graft- and patient-survival data have not been calculated by UNOS, OPTN, or the Scientific Registry.

Graft survival refers to the percentage of transplanted organs that are still functioning at a given time point after transplant. Patient survival refers to the percentage of patients who are alive at a given time point after transplant. In this report, graft and patient survival rates are provided at 1 month, 1 year and 3 years.

Survival rates are based on the observed percentage of grafts or patients that survived for a specified period of time after the transplant. The actual survival rate is valuable information, but it can be misleading by itself because survival depends on both the effectiveness of the services within each individual transplant program and the characteristics of each individual patient within each program.

Source: UNOS Transplant Patient DataSource, 2001.

One report discussed by Dr. Roland came from the University of Minnesota and was published in 1991 (Erice, 1991). Data collected from five HIV-positive transplant recipients at the University of Minnesota were studied with data from 83 reported cases of HIV-infected organ recipients from other centers. Sixty-six of the 88 patients were HIV-negative before transplantation and received organs or transfusions of blood from individuals who were positive for HIV.

Twenty-five (28%) of the 88 patients developed AIDS, and 20 of the 25 (80%) died of AIDS-related complications approximately 37 months after transplantation. Another nine patients (10%) developed other HIV-related diseases. The mean time of progression to AIDS was 27.5 months among all patients with AIDS. For patients who were HIV-negative at the time of transplantation, the mean time of progression to AIDS was 32 months, whereas patients who were HIV-positive before transplantation developed AIDS within 17 months.

Transplant-specific data are also available from the University of Minnesota review. Among patients receiving a kidney transplant, 48 were infected with HIV in the perioperative period. Thirty-seven of these 48 kidney recipients reported graft function, and 76% of these had normal graft function. After a mean follow-up time of 35 months, 13/48 (27%) patients developed AIDS, 7 (15%) developed symptomatic HIV, and 28 (58%) were asymptomatic. There were 13 deaths during the follow-up time, 11 (85%) in people with AIDS.

Of the 11 patients who received a kidney transplant and were HIV-positive at the time of surgery, eight reported graft function, 6 (75%) of which were normal. After a mean follow-up of 31 months, 3 (27%) patients progressed to AIDS and 8 (73%) remained asymptomatic. Among the four deaths reported, three occurred in people with AIDS.

As for liver recipients, 12 patients were HIV-negative at the time of transplantation. Eleven of the 12 (92%) patients had normal graft function. After 37 months, 3 (25%) developed AIDS, 2 (17%) developed symptomatic HIV, and 7 (58%) remained asymptomatic. Four deaths in this cluster were reported, two of which occurred in asymptomatic patients. The ten patients who were HIV-positive at the time of transplantation did worse—approximately 40% had AIDS 19 months post-transplantation and nine died approximately 14 months after the liver transplant. Five of the nine deaths were in asymptomatic patients and resulted from sepsis, aspiration, drug toxicity, or excessive blood loss during surgery.

Another report discussed by Dr. Roland was published in 1994, this time by an infectious disease team at the Hopital Bichat-Claude Bernard in Paris (Bouscarat, 1994). Eleven HIV-positive liver recipients were included in the report, all of whom acquired the infection between 1985 and 1987. Eight patients were infected by blood or blood products from

graft-related transfusions and one by the graft itself; the remaining two patients were infected after transplantation as a result of independent risk factors. All patients received a triple-drug immunosuppressive regimen including cyclosporine.

After a mean follow-up of 52 months, chronic graft rejection was documented in four cases. The cumulative incidences of HIV-related complications and HIV-related deaths were 82% and 27%, respectively, and three patients died rapidly from HIV-related complications. Encouraging, though, was the seven-year survival rate reported: 36% among the 11 perioperative-infected patients and 70% among the patients infected after transplantation.

A third report, published in 1990, involved 15 HIV-positive liver recipients (Tzakis, 1990). After a mean follow-up of 12.75 years, 2/15 (13%) patients were still alive, one of whom was infected prior to transplantation and one of whom was infected perioperatively. Interestingly, both patients who are still alive began HAART within the years following transplantation. Of the 13 patients who died during the follow-up period, only one reported using HAART.

The Pittsburgh Experience

ONE OF THE MORE PROGRESSIVE TRANSPLANT surgeons is Dr. John Fung at the University of Pittsburgh. Dr. Fung and his colleagues have been conducting organ transplants in HIV-infected patients for several years, both before and after HAART entered the treatment vernacular. "The Pittsburgh group deserves a lot of credit," offered Dr. Roland. "Their work in HIV and transplantation has moved this whole field forward."

Anecdotally, Dr. Fung has reported his experience with five liver-transplant patients and two kidney-transplant patients, all of whom were receiving HAART prior to transplantation. Coincidentally, the five liver recipients were receiving a protease inhibitor-based regimen, and the two kidney recipients were receiving a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen.

Tacrolimus was the calcineurin inhibitor selected by Dr. Fung to treat these patients postoperatively. "This drug needs to be used carefully in patients receiving either a protease inhibitor or an NNRTI," cautioned Dr. Roland. "Protease inhibitors increase tacrolimus levels dramatically. In patients receiving a protease inhibitor, tacrolimus is being dosed by Dr. Fung at one to two milligrams a week. For patients receiving an NNRTI, there is still a need for caution, and the dose used in Pittsburgh was 0.1 mg/kg/day."

To date, Dr. Fung has reported one death and one case of chronic rejection. "The circumstances behind this unfortunate rejection case should give us pause," Dr. Roland said. "During his recovery, the patient's doctor initiated an antiretroviral-drug holiday. The patient had stopped taking his protease inhibitor, and this was not reported back to the transplant team. Because there was no longer a P450 interaction during this time, the tacrolimus dose was too low. Communication among all clinicians and the patients and careful watching for drug interactions is a must."

Four of the liver recipients are still alive, all of whom underwent transplantation because of HCV-associated liver disease. The fifth patient underwent transplantation because of NRTI-induced hepatic failure and died shortly after the procedure. The longest follow-up time has been 2.5 years for one of the liver recipients. Unfortunately, three of the four liver recipients have experienced a recurrence of HCV. Treatment with interferon-alpha and ribavirin (Rebetron) was initiated in all three patients, and one patient has since remained HCV-RNA negative.

With respect to HIV progression, all transplant recipients have maintained an undetectable viral load and now have CD4+ counts above 200 cells/mm^3. "We're all encouraged by the lack of HIV disease progression in these patients," Dr. Roland said. "There haven't been any viral rebounds and the CD4+ cell counts are holding strong. The clincher is the two-and-a-half-year survival in one of his patients. We're not sure if we'll see this in the UCSF study, but it's definitely what we're after."

The UCSF Study

THE OBJECTIVES OF THE UCSF STUDY—NAMED the Midgen HIV Transplant Initiative after Carole Midgen, the California assemblywoman who pushed for funding of the project—are clear and concise. The first objective is to evaluate the impact of kidney and liver transplantation, and post-transplant immunosuppression, on HIV disease progression and markers of immune function. Another issue to be looked at will be the impact of HIV infection on graft function and survival. The third objective built into the study is to evaluate the pharmacokinetic interactions between immunosuppressive agents, the protease inhibitors and the NNRTIs.

Eligibility criteria for inclusion in the study are not out of the ordinary. Prospective patients must meet standard listing criteria for placement on transplant waiting lists. Patients must not have had opportunistic infections in the past—with the exception of esophageal candidiasis—and must be willing to use prophylaxis against PCP, herpes, and fungal infections as indicated. Those receiving transplantation because of HCV infection must be willing to undergo frequent monitoring, including liver biopsies and treatment of HCV in the event of recurrence. Both pediatric and adult HIV-positive patients are eligible for enrollment.

CD4+ cell count and viral load criteria vary for potential kidney and liver recipients. Kidney transplant recipients must have been on a stable antiretroviral regimen for three months prior to study entry and have an undetectable viral load (<50 copies/mL) and a CD4+ count of at least 200 cells/mm^3. Liver recipients must have a CD4+ count of at least 100 cells/mm^3. Patients are also required to have an undetectable viral load while on a stable regimen.

Patients will be followed for five years. Most follow-up visits will take place in an outpatient setting, with the exception of five inpatient visits to the General Clinical Research Center (GCRC) for the necessary pharmacokinetic studies. Of course, patients who experience organ rejection or require medication-dosing adjustments will be hospitalized in the GCRC for additional PK monitoring.

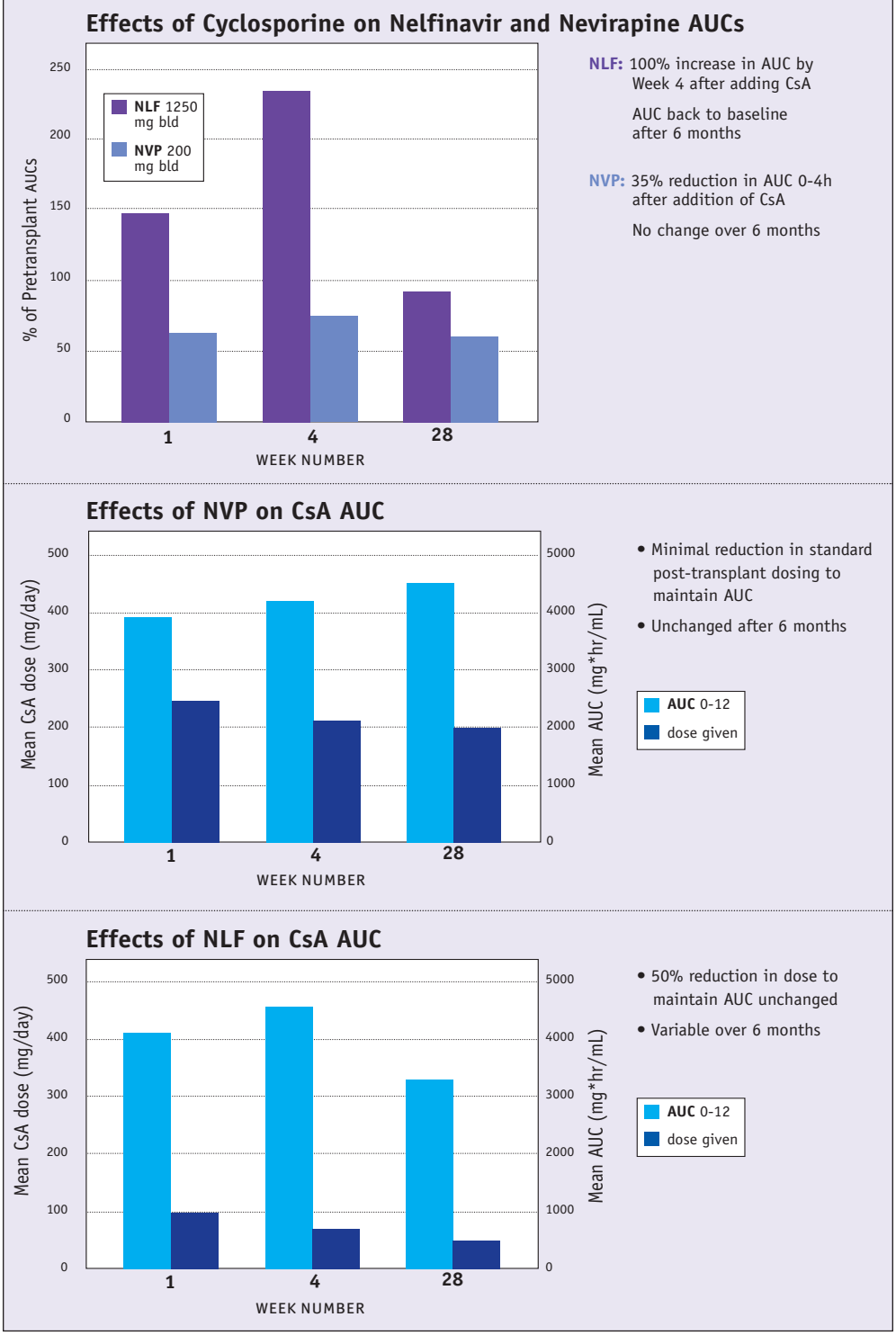
The immunosuppressives used in the study are similar to those used in standard transplantation cases. Prednisone, mycophenylate, and a calcineurin inhibitor (either tacrolimus or cyclosporine) can be used. Of course, the calcineurin inhibitor dose will depend on P450 interactions and patients. Moreover, providers and patients will be alerted to the fact that mycophenylate and stavudine or zidovudine are possibly antagonistic and that concomitant use should be avoided when possible, given issues of resistance and tolerability.

Dr. Roland noted that the use of calcineurin inhibitors in HIV-positive patients

Preliminary pharmacology data from the UCSF Midgen HIV Transplant Initiative were reported at the 8th Conference on Retroviruses and Opportunistic Infections by Dr. Roland. Analyzed thus far have been data regarding the interactions between the calcineurin inhibitor cyclosporine and the antiretroviral drugs nelfinavir (Viracept) and nevirapine (Viramune). Additional pharmacology data will be reported as the study continues.

Source: Roland M, Stock P, Carlson L, et al. Solid organ transplantation in HIV disease [Abstract 579]. 8th Conference on Retroviruses and Opportunistic Infections, Chicago, 2001. Reprinted with permission.

Figure 1. Cyclosporine (CsA), Nelfinavir (NLF), and Nevirapine (NVP): Preliminary Interactions Data



is interesting. Calcineurin inhibition, particularly cyclosporine, halts CD4+ cell proliferation. While on one level this may seem counterproductive, slowing CD4+ cell proliferation actually decreases the number of available HIV targets. "There have been retrospective reviews indicating that certain immunosuppressive regimens decrease HIV-disease progression," Dr. Roland explained. "We're not sure why this is, but it may be that these drugs decrease immune system over-activation, one of the hypothesized mechanisms associated with HIV infection. Cyclosporine is also believed to have direct anti-HIV activity through interactions with cyclophilin."

Four substudies have been built into the Midgen HIV Transplant Initiative. The first is the pharmacokinetics assessment. Patients will be admitted to the hospital and plasma samples will be evaluated over 24 hours for immunosuppressant, protease inhibitor, and NNRTI concentrations (see Figure 1 for preliminary drug-drug interactions data reported at the eighth Conference on Retroviruses and Opportunistic Infections in February).

Urine toxicology screening will also be conducted to look for illegal and other prescription drugs, not for study exclusion, but for other drug-drug interactions.

The second is a study of human papillomavirus (HPV) or, more specifically, the development of cervical or anorectal dysplasia and neoplasia in the transplant recipients. Dr. Roland explained that, "people with HIV and patients who receive transplants are at an increased risk for the development of cervical and anorectal dysplasia. We want to make sure that transplantation in HIV-positive patients doesn't accelerate this process even more. We'll be following clinical and pathologic signs of dysplasia and carcinoma with serial colposcopic exams, Pap smears, and biopsy if indicated."

The third substudy involves human herpes virus-8 (HHV-8), the virus believed to be the cause of KS, Castleman's disease, and body cavity-based lymphomas. Patients will be tested for HHV-8 and quantitative HHV-8 viral load in blood plasma and cells; immunologic studies related to HHV-8 will also be conducted.

The fourth substudy will look at the immunologic consequences of transplant and immunosuppression in the patients enrolled. The immunologic parameters to be

evaluated include, but are not limited to: peripheral blood phenotyping to assess the composition of circulating subpopulations of lymphocytes (e.g., naive vs. memory cells); lymphocyte proliferative response (LPR) assays to asses changes in response to alloantigen, phytohemagglutin, and recall antigens; natural killer cell function; CD8+ cell-suppressing activity; chimerism studies; and chest CT scans to assess thymic index.

The current level of funding from the State of California will only enable UCSF to provide clinical and research evaluations for approximately 15 recipients of kidney or liver transplants, all of whom must be California residents. While funds are available to cover the costs of transplantation, Dr. Roland and her team are working closely with third-party reimbursement programs to encourage them to cover the clinical costs. "This will allow us to stretch our funding dollars and cover as many interested and eligible HIV-positive patients as possible, and learn as much as possible by maximizing the research opportunities."

To further the goals of this pilot study, Drs. Roland and Stock have been working with clinicians and investigators from around the country to put together a multisite study with a common protocol and a centralized data collection and analysis facility. The National Institutes of Health have kicked in approximately $300,000 to help pay for data collection and lab work, but the bulk of necessary funding will need to come from private insurers to cover the costs of transplantation surgery and postoperative care.

Initial Experiences

AT THE TIME OF DR. ROLAND'S NOVEMBER PRN lecture, five HIV-positive patients had received transplants in the UCSF study. All patients are still alive, and the longest follow-up reported by Dr. Roland was 27 weeks for the first patient enrolled.

The first patient, a 15-year-old male who was coinfected with HCV and HIV, received a liver-lobe donation from his mother. After transplantation, decompensated liver disease occurred, and a second transplant—involving a cadaveric liver and kidney—was performed. The remaining four patients all received kidney transplants, one from a living donor and the other three from cadavers. "They're all doing quite well," offered Dr. Roland in her closing remarks. "All of them, with the exception of the first patient, have been able to maintain undetectable viral loads and have CD4+ counts about 200 cells/mm^3. We're now screening several patients and we're expecting to produce some interesting data in the months and years to come." prn

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REEFER MEDICINE AT UCSF

PRELIMINARY DATA FROM THE MIDGEN HIV Transplant Initiative (see Figure 1 on page 22) was not the only poster presentation out of the University of California, San Francisco (UCSF) to stop traffic at the 8th Conference on Retroviruses and Opportunistic Infections. Also presented by two UCSF teams were results from what may be the first prospective clinical trial of its kind: a controlled study of marijuana smoking involving HIV-positive people.

Despite the fact that marijuana has a long history of use—whether it's recreationally or medically to boost appetite, control pain, or counter drug side effects—there has been little scientific evaluation of the herb's potential benefits and drawbacks in people living with HIV. Thus, two poster presentations at CROI—focusing on the short-term safety of marijuana smoking and its potential drug interactions—were a sight for sore eyes.

Conducted at the UCSF General Clinical Research Center, the study randomized 67 patients—all of whom were monitored on an in-patient basis for 21 days—to receive either quality controlled marijuana cigarettes, dronabinol (Marinol) 2.5mg, or placebo three times a day before meals. More than half of the patients had <50 HIV-RNA copies/mL upon entering the study; 30 patients were being treated with an indinavir-based regimen and 37 were being treated with a nelfinavir-based regimen.

There was no significant change in HIV-RNA levels or CD4+ or CD8+ cell counts during the study. There was, however, a non-significant decline in serum testosterone levels in both the marijuana (-73.8 ng/dl) and dronabinol (-40.9 ng/dl) groups. As for side effects, there were three grade 2 or 3 on-study adverse experiences in the marijuana and dronabinol groups, with none in the placebo group.

Also of interest was the reported effect of cannabinoids on plasma concentrations of indinavir and nelfinavir. Smoking marijuana decreased the indinavir AUC by 24% and the nelfinavir AUC by 17%; the reported C_{max} decreases were 21% and 14% and the C_{min} decreases were 22% and 17%, respectively. These changes were statistically significant, compared to minimal concentration changes in the dronabinol and placebo groups.

Although these statistically significant decreases in protease inhibitor concentrations were observed, the study authors concluded that they seem to have minor short-term clinical consequence. It is not known, nor is it really expected, that these pharmacokinetic changes will confer long-term clinical significance. The authors were also encouraged that marijuana smoking did not have a significant effect on viral load or CD4+ counts, at least in this short-term study. prn

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