

# The amfAR Treatment Insider

## Treating HIV in the 21<sup>st</sup> Century

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## Attacking HIV on All Fronts

by Dave Gilden

“The drugs are overrated,” commented Dr. Zvi Grossman of Tel-Aviv University during a question period at April’s Keystone Symposium on Novel Biological Approaches to HIV-1 Infection. Dr. Grossman, who presented a poster at the conference modeling residual HIV replication despite maximally suppressive drug therapy, was responding to conference presentations that bore out his viewpoint. Even when highly active antiretroviral therapy (HAART) seems successful, there is persistent low-level HIV replication and a long-lived reservoir of cells latently infected with HIV. That reservoir outlives everyone’s expectations and perversely refuses to die, reported Johns Hopkins researcher Robert Siliciano. Anthony Fauci, one of the NIH’s chief HIV experts, opened the conference by relinquishing all hope that present therapies could ever cure HIV infection. Rather, he advocated periodic treatment interruptions as a way of teaching the immune system to effectively control the virus.

“The immune system is overrated,” responded Roger Pomerantz of Thomas Jefferson University in Philadelphia. Later, the conference heard Andrew McMichael from Oxford expound on the potential for HIV to mutate and elude effective immune control just the way it breaks free of effective drug therapy. This doesn’t happen often, though, probably because the

immune system rarely effectively restricts HIV, letting the virus progressively devastate the body’s immune capabilities rather than the other way around. Then, there was Paris researcher Brigitte Autran’s new observation that her patients’ HIV-targeting CD4 T-cells decline further with each treatment interruption. Once again, HIV was winning the battle.

Without effective immune control, persons infected with HIV are faced with lifelong therapy. Medical research as a result is engaged in a constant race to keep ahead of the virus. New drugs are required and old ones dropped each time HIV develops resistance or long-term side effects become intolerable. When there are no new agents to prescribe its as if the clock were turned back to 1995. This disagreeable prospect bears little relationship to the optimism voiced four years ago at the dawn of HAART. In those days, adventurous patients were beginning to stop therapy after a year or so with the idea that they might finally be free of the HIV nightmare.

Given the atmosphere of disappointment, it is little wonder that AIDS “dissidents” such as Celia Faber or Nicholas Regush have recently gained wide publicity for their theories that antiviral drugs, not HIV, are the fatal factor in AIDS. Others, meanwhile, renew their interest in such alternatives as herbal therapy that promise

### Commentary

nontoxic, “natural” ways to counter HIV’s impact and rebuild the immune system.

Holistic health is overrated, too. There is evidence that vitamin supplementation and exercise prolong survival, at least in the absence of HAART. That makes sense because these two support the body’s overall metabolic activities, which are sorely taxed by chronic HIV infection. But the holistic concept that merely supporting the body’s natural immunity will eliminate disease plainly does not work with HIV. Unless the immune system is finely tuned to suppress the virus, a vigorous immune defense ironically helps HIV by providing more activated cells in which it can massively multiply. “More food for the virus,” as they say.

By chance, a few people do succeed in curbing HIV on their own. They never need antiviral drugs, and they could provide a model for the rest of everyone else with HIV. About 1% of persons with HIV keep their viral loads generally under 50 copies/mL and never progress to AIDS. An NIH study released in March found that these permanent nonprogressors usually have a peculiarly narrow range of killer cells (CD8 cytotoxic lymphocytes or CTLs) that hunt down HIV-infected cells. Conventional wisdom would consider this immune defense ineffective because it leaves open to many opportunities for HIV to mutate and evade detection.

The key to success here seems to lie in a genetic ability to flag HIV-infected cells in a particularly efficient manner. Such marking allows the immune system’s killer cells to quickly eliminate infected cells before HIV has a chance to replicate and spread. (Eleven of the 13 nonprogressors studied had a gene known as HLA B\*57. It helps determine the nature of the receptors on cell membranes that display the products of a cell’s viral infection and signal the CTLs to attack.) Still, not everyone with this genetic makeup can contain HIV, so other factors must come into play in the first months of infection.

The body needs help, and here modern medicine steps in with its precise theories of HIV pathogenesis. Researchers spent the first two days at Keystone thrashing out the details by which HIV enters new cells and integrates its genes into the cells’ tightly wound spools of DNA. Many in the audience found this tedious, but it is necessary for sorting out how HIV diverts normal cell processes to its own advantage. That in turn can lead to more precise ways of protecting cells

with fewer damaging side effects. We may have long to wait for such innovative approaches: Dr. Peter Kim of MIT complained bitterly in his address on fusion inhibitors about ongoing corporate disinterest in his novel compound. The large pharmaceutical companies stay with the tried and true. In the case of HIV, this means inhibitors that jam up the workings of the HIV enzymes – reverse transcriptase and protease and, maybe, integrase.

When antiviral therapy is successful, it creates a whole new biological environment. The immune system can recover from HIV’s destructive effects, and immune modulating therapies can proceed without fear of feeding the virus’ voracious appetite. Then the question is whether our understanding of immunity is sufficient to help the body mimic the success of the natural nonprogressors.

At Keystone, Brigitte Autran supported combining HAART with therapeutic vaccines plus cell signaling molecules (cytokines) like IL-2. These would create a population of activated CD4 and CD8 killer cells that specifically hunt down cells containing HIV.

Mike McCune of the Gladstone Institute in San Francisco gave a lecture on the way the thymus, a gland at the base of the neck, rebounds in adults on HAART to replace the depleted CD4 cell population. Administering IL-7, a cytokine that promotes thymus function, could help the thymus produce more such cells to fill in the holes in the repertoire of immune responses caused by HIV.

Finally, there was Robert Gallo, who proposed using what is perhaps a regulator of initial fetal development to suppress HIV and cancer, too. That is not so illogical, since both are the expression of errant genes.

Once there is viral suppression and a strategy to induce HIV-controlling immunity, then it is possible to talk about the overall support that the body needs to maintain that response. By progressing from the level of the virus (chemotherapy) to the immune system (biologic modulators) to the body as a whole (nonspecific health-enhancing measures), we create an integrated therapy that ranges from hard technology to soft technology. Supporting the body’s regenerative efforts and fine-tuning the immune defense against HIV while drugs keep the virus suppressed: This multitier strategy could eventually wean persons with HIV off therapy altogether.

*A few people do succeed in curbing HIV on their own, but overall the body needs help on many levels.*

## Keystone Conference Hunts for Immune Strategies

by Jo Anne Berg

This year's HIV Keystone Symposium, held in Keystone, Colorado on April 4-10, brought together some 450 scientists in an attempt to break the current impasse in HIV therapy. Entitled "Novel Biological Approaches to HIV-1 Infection Based on New Insights into HIV Biology," the event largely focused on the loss of immunity triggered by HIV. Many scientists believe this loss will require immune-based therapies to supplement antiretroviral drugs.

### Confusion Reigns Where HIV and Immunity Meet

Anthony Fauci,<sup>1</sup> who heads the NIH's National Institute for Allergy and Infectious Diseases, laid out one of the major conundrums in a keynote address. He explained that newer assays show that more HIV-specific CD4 T-helper cells are present after the initial, acute phase of HIV infection than previously thought. These cells should organize the immune system's defense against the invading virus. Perversely, they do not proliferate as they are supposed to when they encounter HIV, although they retain the ability to produce cell-activating cytokines. (Cytokines are hormone-like proteins that cells secrete to communicate with each other.) Fauci said that this discordance between nonproliferation and the ability to express proliferation-associated cytokines does not represent a phenomenon unique to HIV. It is seen in other diseases involving a hyperactive immune system. On the other hand, one Keystone poster<sup>2</sup> argued that "anergy and even death of most HIV-specific CD4 may be interpreted as a 'good' response, protective against an explosive spread of HIV (such as occurs in the acute phase.)"

HIV may have several means of evading immune control. Warner Greene,<sup>3</sup> director of the Gladstone Institute in San Francisco, said he was surprised to find that "at the peak of HIV infection, few HIV-infected cells are apoptotic." (There are two normal kinds of cell death. Aged cells die of necrosis, and cells that become dysfunctional or superfluous are eliminated by a form of cellular suicide, or apoptosis.) He explained that a function of the HIV Nef protein may be to signal uninfected T-cells that come into contact with those that are infected to undergo apoptosis. On the other hand, Nef can also protect the infected cells from apoptosis, ensuring that they survive long enough to produce a new generation of HIV.

Susan Zolla-Pozner<sup>4</sup> of New York University announced a newly discovered way that HIV envelope protein, known as Env or gp120, can subvert the immune system's response to it. HIV-specific CD4 T-helper cells, particularly those that would promote an immune response to Env, seem weak or absent in most persons with HIV. She questioned whether anti-Env antibodies might be negatively affecting this response, since she recalled a study showing that HIV-exposed but uninfected individuals (EUs) had a good CD4 T-helper cell response to Env but no anti-Env antibodies.<sup>5</sup> The T-helper cells sensitive to Env quickly vanish if an EU does become infected after another exposure to HIV and starts producing antibodies to the virus. She found that antibodies to a specific part of the Env protein "turn off the ability of antigen presenting cells [such as macrophages and dendritic cells] to present gp120 to T-cells and the ability of the T-cells to respond to that presented antigen."

The disruption in immune function seems to stem from antibodies against the critical "CD4-binding domain," the portion of gp120 that binds to the CD4 receptor as HIV prepares to infect a new cell. Somehow these antibodies induce the antigen-presenting cells to stop signaling T-helper cells that HIV remains in the body. (Antigen-presenting cells capture foreign microbes

and break them up so as to display some of their protein fragments in receptors on their surface. They search for CD4 T-cells that can recognize the particular antigen-receptor combination and prime those cells to proliferate.)

Zolla-Pozner noted that her laboratory observations could help explain the lack of disease progression in certain individuals with good Env-specific CD4 responses but no anti-Env antibodies. Her lab will now investigate other HIV antibodies and other CD4 T-helper cell responses to HIV to see whether similar interference occurs.

Another newly found way HIV may use the antigen-presenting process to its advantage involves the extremely efficient dendritic cell (DC). Yvette van Kooyk<sup>6</sup> of the University of Nijmegen in Holland explained that her group recently rediscovered a protein first identified in 1992 by its strong binding to HIV Env. They found that this protein, DC-SIGN, is an adhesion molecule that aids in the interaction between dendritic cells and CD4 T-helper cells.

Van Kooyk believes that HIV is able to latch onto DC-SIGN and thereby hitch a ride to the CD4 T-helper cells concentrated in the lymph nodes. Her group is still unsure of the mechanisms by which DC-SIGN ferries and

*HIV has many ways of evading immune control.*

transmits HIV to the cells in the lymph nodes. HIV may be internalized after it attaches to DC-SIGN, protected during its “ride” inside vesicles.

The ability to block the HIV/DC-SIGN coupling would be especially important just after exposure to HIV, when HIV is confined to mucosal surfaces in the genital tract or rectum and needs a mechanism for reaching cells that it can infect. Vaccines that evoke special antibodies or new microbicides might stop the binding of HIV to DC-SIGN.

Researchers believe that DC-SIGN binds to HIV via the mannose sugars attached to Env. Early in all infections, the liver produces mannose-binding protein (MBP) to bind to sugar molecules on invading pathogens, marking them for destruction. Interestingly, older studies<sup>7</sup> found an inverse correlation between MBP levels and viral load. The new DC-SIGN finding suggests that MBP might bind to HIV and prevent it from latching onto DC-SIGN. Scientists at Keystone believed that ways to enhance MBP should be explored. A Keystone poster<sup>8</sup> noted that “high-mannose oligosaccharides constitute a target structure for cyanovirin-N (CV-N),” a protein isolated from blue-green algae. Thus, CV-N might work similarly to MBP and is a promising anti-HIV microbicide candidate. The developers of CV-N are also exploring ways to apply their discovery to a systemic therapeutic agent.

Christopher Miller<sup>9</sup> of the University of California Davis presented further observations concerning dendritic cells’ role in the first few days of infection. These contradicted van Kooyk, who argued that HIV did not actually infect the dendritic cells. Miller vaginally inoculated monkeys with SIV, the simian version of HIV. His sensitive virus assay (which involves radioactively labeling HIV genes) detected dendritic cells in the vaginal epithelium that were infected by HIV and producing new virions. By his estimate, around 10,000 dendritic cells become infected in the first 18 hours after inoculation, even before macrophages and CD4 T-cells become infected. He thinks that this rapid accumulation and subsequent dissemination to the lymph node creates extra hurdles for a successful preventive vaccine, but it does stress the importance of stopping HIV immediately after exposure.

### Immune Restoration with Biological Therapies

Robert Gallo,<sup>10</sup> who now directs his own laboratory at the University of Maryland, described a 35 amino acid peptide dubbed “maternin” that is derived from human chorionic gonadotropin (HCG, a hormone found in the urine of women early in pregnancy). Gallo has been

researching the therapeutic effects of HCG for many years. He said the effects of the maternin derivative are “far greater and broader than we ever thought,” noting a dramatic improvement in pulmonary Kaposi’s sarcoma after treatment with this substance. There also are indications that maternin induces apoptosis of cancer cells. Gallo called it “more potent than the cancer drug taxol.” Furthermore, transgenic mice that contain HIV genes die in infancy. But the same transgenic mice given maternin “thrived,” according to Gallo. Likewise, SIV-infected macaque monkeys treated three times a week subcutaneously with the peptide had gains in weight and CD4 numbers.

There was a rise in CD4 T-cell numbers in uninfected macaques, too. Gallo believes that a vital clue to maternin’s mechanism of action is its presence when the early human embryo is developing rapidly. He believes the peptide enhances hematopoiesis (ability to produce new blood cells) by acting as a growth factor. To document this action, Gallo’s group gave lethal doses of radiation (which destroys hematopoiesis) to rats with and without maternin. All of the controls died within five days, whereas 100% of the peptide-injected group survived up to four months.

Maternin’s reputed regulatory effect on gene expression and cell maturation may explain its anti-HIV and anticancer effects, but there have been no trials yet to test whether it is active within the human body and the immune dysfunction that is a hallmark of HIV infection.

Michael McCune,<sup>11</sup> also of the Gladstone Institute, spoke on another central aspect of that dysfunction – the inability of the thymus gland to maintain the level of new, “naïve” CD4 T-helper cells during HIV infection. He believes that low CD4 counts are due both to accelerated destruction by HIV and to what he calls “regenerative failure” by the thymus. McCune suggested that “efforts should continue to focus on the problem of [regenerative failure], and the solution... may be to find a way to restore and/or to promote the function of the thymus.” The cytokine IL-7, which helps stimulate thymopoiesis (production of new naïve T-cells within the thymus), could be helpful here. Its drawbacks are that it also promotes lymphoma and HIV replication.

Another cytokine featured at Keystone was IL-2, with mixed reviews. Norman Letvin<sup>12</sup> reported that his group had found the addition of an IL-2 gene to a DNA vaccine against SIV improved antibody responses 30 times over the antibody response of animals given the DNA vaccine only. (In a DNA vaccine, an innocuous mock viral infection is created by a portion of a pathogen’s gene set. These genes are taken up by a few

*Maternin, an extract from the urine of pregnant women, could suppress HIV, tumors....and radiation sickness.*

cells and stimulate new immune responses as they start to produce the proteins they encode.)

At a pre-HIV Symposium lecture, however, noted British immunologist Phillipa Marrack<sup>13</sup> announced that she has discovered that IL-2 can function to shut down memory cells, including the CD8 or cytotoxic T-lymphocytes that are most instrumental in removing HIV from the body. In a paper now in press, she declares her belief that IL-2 should not be used in HIV disease. Also, an update<sup>14</sup> on the way HIV's core protein, Gag, binds to a cellular product called cyclophilin A hinted that one of the reasons for this unexplained binding might be to enable HIV to take advantage of the large amounts of IL-2 expression induced by the binding.

Fauci reminded his audience that his laboratory's experience with IL-2 was mixed. Patients on IL-2 plus potent antiviral therapy achieved normal CD4 counts, and a few seemed to have emptied their reservoir of latently infected cells, perhaps because of IL-2's activating effect on those cells. But when these patients' therapy was stopped, the IL-2 recipients experienced the same rapid viral rebound as those who had never received IL-2. Fauci is now pursuing structured treatment interruptions (two months on HIV therapy, one month off) as a promising strategy for taking advantage of viral rebounds to boost functional immunity against HIV.

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9. Miller CJ. Rapid Infection of Intraepithelial Dendritic Cells after Intravaginal Simian Immunodeficiency Virus (SIV) Exposure. HIV Keystone Symposium. April 4-10, 2000; oral presentation 037.

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11. McCune JM. Maintenance of T Cell Homeostasis during the Course of HIV Disease Progression. HIV Keystone Symposium. April 4-10, 2000; oral presentation 033.

12. Letvin NL. SHIV Model. HIV Keystone Symposium. April 4-10, 2000; oral presentation.

13. Marrack P. T Cells Alive or Dead. Keystone Millennium Symposium. March 31-April 4 2000; oral presentation.

14. Luban, J. HIV-1 Requires Cyclophilin A for Wildtype Replication Kinetics. HIV Keystone Symposium. April 4-10 2000; oral presentation 014.

## Remune Trial Results from Thailand

Antiviral drugs' cost makes them generally unavailable in developing countries, creating a special challenge for immune-based therapies. The placebo-controlled Remune trial in Thailand tested this killed HIV vaccine alone in 297 otherwise untreated persons with HIV. Participants had an average CD4 count of about 450 cells/mm<sup>3</sup> at study entry. They were inoculated every 12 weeks.

It is questionable whether a vaccine will work under these conditions. Untreated persons with HIV already have large amounts of the virus, so a little extra may not make much difference. The Immune Response Corporation, which makes Remune, has argued that the adjuvant included in the vaccine has a critical impact on creating effective anti-HIV immune defenses.

The adjuvant alone served as the placebo in the Thai trial. Average viral load was stable through the 40-week follow-up period in both the Remune and placebo groups. CD4 cell count went up by 84 cells/mm<sup>3</sup> in the Remune group and by 38 cells/mm<sup>3</sup> in the placebo group. Sixty-eight Remune recipients have now gone through 88 weeks of therapy. Twenty of the 68 had viral load decreases of at least 70% (0.5 log), and nine had viral load increases of more than 70%. Viral loads in the rest were more or less stable.

Based on these results, the Immune Response is applying to the Thai authorities for registration of Remune as a first-line therapy for HIV. Remune would be tried alone, with antiviral drugs saved for nonresponders. "Registration is more like expanded access," commented Ronald Moss, Immune Response's chief scientist. "The Thai government could give it to lots of people and see if it has a clinical effect. And if it only works for 30%, it would be worthwhile there."

Back in the US, the ACTG 5057 trial is about to open. It will administer Remune or just adjuvant to 452 persons on combination antiviral therapy who have suppressed their viral loads to below 500 copies/mL. The trial's goal is to check the immune responses conferred by Remune when drugs suppress HIV and see if they decrease or delay viral breakthrough. -DG

## Persons with HIV Struggle for Transplant Access

by Jeff Getty

Alan Hext, a person with HIV who broke new ground when he received a liver transplant in December 1998, is alive and well a full year later. Doctors say that his new liver is functioning perfectly. Hext now weighs a robust 180 pounds, and his CD4 cell count has gone up from around 300 at the time of the transplant to 435. His HIV viral load, meanwhile, remains undetectable. Hext is one of a very few persons with HIV to receive a liver transplant from Pittsburgh University. One other patient survives; two have died.

When one looks at Hext one sees a large, strong, healthy man – not a dying liver or AIDS patient. His amazing survival story recently appeared on the front page of *USA Today*. Hext said that in the last year his health has been fine, with only a few complications from minor infections. He was hospitalized once following an infection arising in the aftermath of a dental abscess excision. Hext now lives in Palm Springs, California with his family and a new baby boy.

Hext's two-year battle to get a liver transplant occurred just as the medical community was beginning to view asymptomatic HIV disease as a chronic manageable illness. Convincing surgeons and insurance companies that healthy people with HIV should be treated like any other chronic disease group was a long uphill struggle for Hext.

### The Growing Demand for Organ Transplants

Various surveys have found that deaths in the HIV community are down 60 to 75% since the 1996 introduction of highly active antiretroviral therapy. Yet certain intractable health problems remain. At the University Hospital of Cleveland HIV clinic, for example, liver and other organ failure accounted for half (16) of the 32 deaths in 1999. (In 1995, 17% (or 19) of 115 deaths were from organ failure.) More and more, patients are facing emerging organ complications as they grow older. Lung infections, cancer, hepatitis B and C, HIV-associated metabolic derangements, and the long-term toxicities of antiviral drugs continue to take their toll. Organ transplants could save many of these people, but transplant doctors have considered patients with HIV too risky a group for their valuable time and precious free organs.

One study carried out in the 1980s under Dr. Thomas Starzl found that people with HIV and AIDS survived

transplants but eventually went on to die from the standard AIDS-related conditions.

The progression to AIDS and death was only slightly more accelerated than the usual course of disease at the time. Even though there were no effective treatments for AIDS or HIV, Starzl concluded that organ transplantation in persons with HIV needed to go forward. The transplant community in general did not accept his opinion, but United National Organ Sharing (UNOS) refused to exclude HIV-positive patients from its organ waiting list.

Dr. John Fung, a leading transplant surgeon at the University of Pittsburgh, was the only surgeon willing to try further liver transplants in HIV patients through the 1990s. Fung's group had always been seen as more radical than the rest of the organ transplant world. His colleagues like to refer to him as a "cowboy." Fung, who is Asian and grew up in Los Angeles, did not have the more traditional conservative views harbored by most organ transplant surgeons.

"I think that anyone who needs a transplant and has a five-year life expectancy should get a chance," he said in a 1996 interview. Fung even advocated that patients on death row should be eligible for transplants if they need a new liver.

Hext was introduced to Fung by advocates from ACT UP/Golden Gate (now Survive AIDS) in San Francisco. At the time, it was becoming painfully clear that he would not get a liver transplant in the state of California. Similar situations were occurring in other parts of the country. Another patient, Gary Bent, checked into a large New York City Hospital with liver failure. Although there was a liver ready for him in the cooler, his surgeons essentially left him to die when they discovered his HIV status at the last minute. An HIV antibody test had been performed without his consent. Bent's family was outraged and filed a formal complaint with the hospital. The hospital was unapologetic, saying that it would have been a waste of a good organ. The family had heard about John Fung and transferred the then comatose patient to Pittsburgh. By the time he arrived, no liver was available, and Bent died shortly thereafter.

Following Hext's denial in San Francisco, activists turned up the heat and staged a large, noisy demonstration on the front lawn of the University of California's Moffit Hospital. A symbolic coffin was placed on the ground and demonstrators formed a picket line. To the hospital's chagrin, public officials and city politicians joined the demonstrators. Shortly after that, the University agreed to move ahead quickly and create a liver and kidney transplant protocol. Anxious to make good, doctors performed a liver transplant on a person

*Transplant center patient Hext now lives in Palm Springs with his family and a new baby boy.*

with HIV in May 1998. But it turned out that the patient had an unsuspected brain disease (PML), and died just two weeks later. By this time, it was clear to all parties that the only way to move ahead with organ transplantation in HIV would be to form a partnership between HIV researchers and organ transplant surgeons.

Under the leadership of Drs. Michelle Roland and Peter Stock, an HIV transplant protocol began to take shape at the University of California San Francisco. The director of the University's AIDS Research Institute, Dr. Thomas Coates (who is himself HIV-positive) took a personal interest in moving the protocol forward. He persuaded the National Institutes of Health to convene a national working group, and several sites began collaborating. At the same time, Dr. Fung was refining his procedures and proceeding cautiously. He also joined the NIH team, and his unit became an NIH transplant site.

The University of California announced in February that a \$1 million grant had been forwarded to its hospital to begin an HIV organ transplant pilot program. UC's press release stated that funds were available to study safety, efficacy and long-term benefits of the organ transplant in seven HIV-infected patients.

Coates has asked the State of California to fund another \$1 million for next year. "Coming out of the recent Retrovirus Conference; rates of cirrhosis and end-stage liver disease double with HIV and Hep C co-infection. Given that the medications are holding... it's essential that we prove as quickly as possible that it's safe for people with HIV to get organ transplants," Coates said. There have been no other large state or federal allocations. Fung and other members of the protocol team are seeking grants and third-party coverage.

### Transplant Availability Still Limited

The nearly complete NIH protocol may always be a work-in-progress. Unlike HIV drug trials, transplant protocols can be adjusted in midstream. The goal is to find a way for as many patients as possible to survive. "Proof of principle is what we are after," commented Fung. There are four sites so far: University of California San Francisco, Mt Sinai Hospital in New York, University of Maryland and Pittsburgh University. "This is really taking off," Coates remarked in a March interview. All four sites are either up and running or close to screening their first patients. Northwestern University is currently considering becoming a site as well.

Unfortunately, none of the sites will get NIH funding to pay for the actual transplants – the NIH does not pay for "procedures." Instead, the sites will rely on private grants and third-party payers. Coates said that the NIH did agree to grant \$150,000 to pay for data collection and some lab work, which will be done free in Chicago, it turns out. Coates also mentioned that he is asking Roche Pharmaceuticals for a grant for more scientific research. Insurance has paid for some HIV-positive organ transplants in the past, and the University of Pittsburgh has become very skilled at obtaining payment.

Coates said that UC will try to stretch its grant money by getting third-party reimbursement whenever possible. With a little luck, UC could complete as many as ten transplants in the next two years. It has asked for funding from the state for next year as well. Dr. Peter Stock, who is a transplant surgeon at UC, indicated that demonstrating the safety of these transplants will establish "proof of principle." Patients can then expect normal third-party payment.

UC's pilot study, which is nearly identical to the other three sites, will be restricted to those patients who have

*Organ failure from toxic drugs or Hepatitis C are becoming leading threats to people on highly active antiretroviral therapy.*

had no major opportunistic infections and whose CD4 cell counts are stable and above 200 for kidney candi-

dates, and over 100 for liver candidates. In both organ groups, patients must have very low or undetectable plasma viral loads (less than 50 copies of HIV RNA/mL) through a strictly followed antiviral treatment regimen. Criteria for other sites may vary in that they will allow lower CD4 cell counts and some history of opportunistic infection. Once a patient has been selected, he or she must go on a waiting list until an organ becomes available. Alternatively, patients can use relatives as donors.

Waiting times vary from site to site. Hext's wait was under one year. Depending on a patient's blood type, the wait in San Francisco could last up to three years.

UC already has received many inquiries from potential organ recipients. "We are getting overwhelmed," said Stock. Stock is concerned that the liver patients will not remain in good health for three years. Stock and Fung are looking into procuring unwanted high-risk organs. Although national waiting list rules are changing so that the sickest patients will always be at the top of the list, some sites may remain reluctant to prioritize HIV and hepatitis C patients ahead of healthier candidates with a better life expectancy.

Dr. Stock says that his site will try to emphasize high-risk organs and living-donor-related livers. In a living-donor transplant, a lobe of a living person's liver is removed and placed in the patient. If all goes well, both

donor's and patient's liver portions will regenerate to nearly normal size in about two months. Such transplants can take place without placing the patient on any waiting list.

## Initial Experiences under the New Protocol

Stock's site in March performed a living-donor liver transplant on a 15-year-old southern California boy. Stock noted that this transplant went quite well, but he warned that these procedures are risky. "We have had two donor deaths nationally so far," he said. Some surgeons will be reluctant to pursue living donors when the patient has both HIV and hepatitis C or B.

The first kidney transplant candidate for the UC study died unexpectedly last fall while still on the waiting list. On April 7, a kidney was transferred from a living donor into a middle-aged HIV-positive man. This operation was a success, and Stock was planning to send the patient home from the hospital soon thereafter.

Several more candidates have been screened and will be placed on kidney waiting lists. At least one HIV patient is now at the top of the waiting list and will most likely receive a new kidney within a month or two. Dr. Robert Scott, an Oakland California practitioner and this patient's HIV doctor, helped get him through the screening process some time ago. "I'm excited. This is a patient who is in good health with 500 CD4. He has HIV-related kidney necrosis," said Scott. "This patient hated dialysis. He was so depressed that he wanted to go off [dialysis] and die." Scott sees this kidney transplant as a life-saving issue – even though there is substantial risk to the first patients. "You deal with risk versus benefit. I think in this case, the benefit outweighs the risk," he remarked.

Pittsburgh has performed four liver and two kidney transplants on HIV patients since 1995. One liver patient died of a postoperative bacterial infection. All the other patients are doing well, according to Fung. Fung's biggest problem has been recurring hepatitis C and B after transplant. He treats the hepatitis C with interferon and ribavirin. Pittsburgh will continue to transplant healthier asymptomatic patients, though probably some of the patients will be a little sicker than the ones UC

will accept. "None of our liver patients had T-cells over 200. Now they have all gone up into the 400s," he mentioned.

Fung has had one patient whose HIV doctor mistakenly took him off a protease inhibitor without checking with the transplant center. Protease inhibitors decrease the body's clearance of antirejection drugs. "The PK [drug level] work here is so critical," Fung remarked. Because antirejection drug levels fell in the patient off the protease inhibitor, his body began rejecting the liver. "That kind of stupid mistake should be avoided," he said.

It is still touch-and-go for this person. Fung believes that they caught the rejection early enough to save the liver, and the patient is improving. Fung and Stock agree that once a patient is transplanted, all medication adjustments must be made through the transplant centers. "Otherwise there may be irreversible damage," said Fung.

## Obtaining Transplants

At least one liver transplant death could have been averted had the patient not pushed so aggressively for the transplant. Once antirejection medication is taken, there is a very good chance that any smoldering unknown infection could break through and cause problems. Liver disease patients need to understand that anyone in a weakened state due to advanced immune dysfunction and opportunistic infections is not likely to survive the transplant procedure. Anyone with HIV considering a kidney transplant might want to wait a year or two if their condition is not life-threatening. Falsifying past medical history and lying to "fudge" into this study could be a deadly mistake.

It is likely that the University of California San Francisco pilot program will have more patients than available slots. Dr. Peter Stock can be reached at UCSF by calling 415/353-1117. Patients who urgently need transplants may also contact Dr. John Fung at the University of Pittsburgh (412/648-3200) and Dr. Barbara Murphy at Mt. Sinai, NY (212/241-5850). Information about the NIH multi-site protocol is available through Dr. Thomas Coates' office (415/597-9175). Patients who have difficulty obtaining help may also contact Survive AIDS at 415/252-9200 to ask for advocacy.

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