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# The Case Against Zerit

*By Bob Huff*

HIV drug therapy works against HIV. This is clear from the dramatic drop in deaths due to AIDS after the use of combination therapy was widely adopted in 1996. But these drugs also act on the body and its metabolism in a number of strange and hard-to-pin-down ways.

In some people—but not all—blood lipids soar to alarming levels that are associated with a higher risk of cardiovascular disease. Yet the rates of heart attack and heart disease in people taking HIV drugs continues to run about the same as those for people without HIV. Antiretroviral therapy may make for some worrisome lab tests, but stopping smoking rather than stopping meds remains a better bet for keeping a healthy heart.

In some people—but not all—fat deposits in the arms, legs and, most visibly, in the face, melt away, leaving people who experience this fat depletion syndrome bearing the tribal scars of facial wasting. When the fat drains from the face, it may be very hard to recover. One option for treating this condition is to undergo an expensive restoration process of soft tissue augmentation using a filler material injected under the skin of the cheeks.

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In some people—but not all—the fat that disappears from their faces and thighs seems to end up in their belly as waist sizes bloom. This isn't really what happens, though, and the type of fat that fills the abdomen, called visceral fat, has different qualities from the subcutaneous fat lost from the face and limbs. And not everyone who gains visceral fat loses subcutaneous fat.

And in some people—but not all—insulin tolerance goes out of whack, which may or may not lead to diabetes. (We won't even discuss bone formation problems.)

If you notice a pattern here, it's that what seems to be a definable lipodystrophy syndrome at the 35,000-foot level, becomes a wilderness of associations and anecdotes once you're on the ground. Inconsistent methods, unvalidated measurements and tiny studies make simply defining this complication contentious as researchers continue to tease out the links between suspected drugs, genetics and HIV itself. So far, no smoking gun has been found and none is expected to turn up. This is, as they say, a multifactorial problem. Scientists looking for answers to this riddle are developing new and more specific lab tests as well as larger and more reliable clinical trials. And clinicians are looking at everything from nuke-sparing regimens to prophylactic glitazones to forestall or minimize the consequences of lipodystrophy. In the meantime, managing the drug-related toxicities of HIV therapy remains an art.

Workers in this ad hoc field recently met in San Diego at the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV to trade notes and argue over epidemiology and favorite pathogenesis theories. For those seeking more than a tantalizing intellectual exercise, there was little to write home about.

### Zeroing In on Zerit

But the weight may be starting to shift on one lingering dispute. For a long time, whenever talk turned to speculation about which drugs were considered prime suspects for causing lipodystrophy, the name of one culprit always came up: Zerit (d4T or stavudine) is a popular nucleoside analog often combined with ddI or 3TC as part of a three-drug combination. The federal HIV treatment guidelines list d4T among its "strongly recommended" choices for first line therapy. Zerit was linked early on with the nerve damage that causes peripheral neuropathy in some people. More recently it's been indicted for contributing to some of the other unpleasant toxicities of ART, such as facial wasting. Of course, a lot of the charges were stimulated by studies and presentations funded by GlaxoSmithKline—makers of AZT and 3TC—who'd love to see this competitor sent away. And most of the counter-arguments and obfuscation originated with Bristol Myers Squibb, the makers of d4T. So, although many people were resolutely convinced of d4T's guilt, controversy held consensus at bay. But this contest may finally be coming to a head—if not a verdict—as the evidence against d4T solidifies. After data presented this year at the annual Retrovirus Conference, at the International AIDS Conference in Barcelona, and now at the Lipodystrophy Workshop and the annual ICAAC conference that followed it a few days later, the strength of the associations between d4T and fat wasting are becoming too strong to ignore. As one observer put it, "You can't really say it's just a Glaxo thing anymore."

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### Mitochondrial Toxicity

The protease inhibitors were the first drug class to take the blame for fat redistribution and lipodystrophy and evidence continues to mount against some of them. But nucleoside analogs have also received scrutiny for their potential to deplete the energy-producing capacity of cells.

The prevailing theory of how nucleoside analogs contribute to fat wasting and elevated lipids revolves around a pathogenic piñata called mitochondrial toxicity. Cellular respiration is the name for a long series of chemical steps in which cells process glucose and oxygen into a useable form of energy. If any of these steps are slowed down or blocked, the whole process backs up and a kind of overflow system starts to consume glucose without oxygen, which dumps a byproduct called lactate into the blood. As an extreme example of what can go wrong with this system, a poison like cyanide can stop cellular respiration dead in its tracks—with rapidly fatal results. But the toxicities thought to be caused by nucleoside analogs are far subtler—so subtle that not all researchers can agree on how, when, where or even if they are happening.

This chain of energy-producing steps takes place mostly within tiny organelles carried inside nearly every cell in the body. These cells-within-cells are called mitochondria, and they possess their own set of DNA instructions to make some of the proteins they need to perform the job of respiration. It's thought that nucleoside analogs —some more than others—can, over time, affect the quantity or quality of several of these crucial proteins by interfering with the replication of mitochondrial DNA. The result can be the generation of excess lactate and an energy deficit in affected tissues; in nerve tissue, neuropathy can be a consequence. Some scientists think a different form of mitochondrial toxicity can trigger a cell to die directly through apoptosis. That could be what's happening to fat cells. Obviously more and better research is needed—fast.

### Looking within the Limits

Researchers have been attempting to find a way to directly measure mitochondrial toxicity by quantifying the amount of mitochondrial DNA that can be recovered from cells. Some of this progress was shown at the Lipodystrophy workshop. But serious objections have been lodged against current versions of this technique because they are liable to contamination from other sources of mitochondrial DNA. Next year, the data from mitochondrial toxicity assays may be more convincing, but for now, they're not ready for prime time.

One blood abnormality associated with ART, and with nucleoside analogs in particular, is an increase in blood lactate levels. Slightly elevated lactate levels are not noticeable, but as lactate levels increase, symptoms such as nausea, abdominal pain and distension may become apparent, causing tolerability problems. Lactate levels over 5mmol/L in the presence of symptoms can indicate a rapidly progressing, life-threatening illness called lactic acidosis. All of the nucleoside analogs have been implicated in this rare lactic acidosis syndrome and every person taking them should know the warning signs: nausea, abdominal pain, fatigue or muscle weakness.

But the meaning of moderately elevated lactate levels, called hyperlactatemia, is not certain, although many people believe nucleoside analog-associated damage to mitochondrial DNA is a cause. Older studies of blood lactates are difficult to interpret because of widely varying methods used to collect and analyze the samples. Adoption of a strict new protocol for the standardized collection and processing of blood lactate samples will hopefully help dispel the fog that has surrounded the meaning of these lab values.

One of the first tipoffs that metabolic abnormalities are afoot is when blood lipid levels start to climb. The key movers are total cholesterol and triglycerides. Rising cholesterol raises eyebrows because of its association with cardiovascular disease—cholesterol can clog the arteries feeding the heart and set off a heart attack. But the underlying metabolic problems causing the cholesterol rise and the role ART plays are still mysteries. The same is true of the rise in triglyceride levels experienced by some people on ART. Sustained high triglycerides may be a predictor for developing pancreatitis or diabetes—and increasing rates of diabetes in people on ART is a growing problem. How and why this is happening isn't certain. Still, most clinicians would feel more comfortable if their patients could achieve decent viral suppression without the abnormal labs.

A number of studies looking at lipid abnormalities have pointed the finger at protease inhibitors and at ritonavir in particular as causative factors. Recently a few more studies have shown that nucleoside analogs add their own bump to cholesterol and triglycerides. And a few high quality studies are starting to examine the associations with actual fat loss and recovery.

Andrew Hill told the Lipodystrophy Workshop that there is a "Tower of Babel" when it comes to reporting drug toxicities in clinical trials, with at least seven different ways of reporting abnormal lab values. Graded levels of toxicity are far less sensitive than using continuous values such as changes in area-under-the-curve. Drug company trials can either hide or accentuate toxicities depending on the method chosen to report events. Often these studies just add to the noise.

### Leaping Lipids

Until recently, most of the research pointing the finger at Zerit used methods that were easy to dismiss, such as small sample sizes, no controls, and uneven reporting criteria. But this latest wave of evidence is not so easily ignored.

A study presented in Barcelona (Gilead 903, sponsored by Gilead Sciences, Inc., the makers of tenofovir) compared d4T with tenofovir in 600 people over 48 weeks. All volunteers received efavirenz and 3TC. It was their first experience with HIV treatment. By the end of the nearly year-long study, viral load reductions were about the same in both groups. But there was a striking difference in the cholesterol and triglyceride levels between those who took tenofovir and those who took d4T. Triglycerides were unchanged from baseline in the tenofovir group but went up by 74mg/dl in the d4T group. Cholesterol also went up by 24mg/dl in the tenofovir group but increased by twice that amount in the d4T group.

More data from Gilead 903 on the lipid profile of tenofovir versus d4T was presented at ICAAC by Joel Gallant of Johns Hopkins University. This trial is scheduled to run for three years—which counts as long-term compared to most studies, but is little more than a honeymoon in terms of how long most people will be taking these drugs. So far—one year in—only lab toxicities have been observed. Gallant made a point of stressing the need for longer-term studies to help accumulate data that might finally correlate lab values with clinical outcomes.

Earlier in the year, a Glaxo-funded study (ESS 40002) showed similar findings at the Retrovirus Conference. As a part of this trial, 111 treatment-naïve patients received nelfinavir plus 3TC and either AZT or d4T as the third drug in their regimens. With nelfinavir in the mix, some increases in cholesterol and triglycerides would be expected. But while people receiving AZT had cholesterol increases averaging 32mg/dl, those on d4T had average increases of 45mg/dl. For triglycerides, the results were even more striking with the AZT group seeing a bump of 31mg/dl while the d4T group saw an average increase of 69mg/dl—over twice as much.

### Lactates in the Dock

In addition to looking at cholesterol and triglycerides, the Glaxo-funded ESS 40002 study also recorded lactate levels at baseline and after 48 weeks. While people taking AZT experienced an average lactate increase of 2.3mmol/L, those on d4T had increases over three times higher, at 7.9mmol/L—well into the danger region.

Another Glaxo-funded study presented at ICAAC (TARHEEL) looked at what happened when treatment-experienced patients who had been on a regimen containing d4T and were experiencing lipodystrophy switched to either AZT or abacavir. A subset of 16 people with elevated lactates stopped all treatment until blood values showed a return to safer levels. At that time treatment was restarted without d4T. At 48

weeks lactate levels remained controlled within a normal range. Although this small substudy lacks a control arm for comparison, the results give guidance to a clinician seeking to normalize hyperlactatemia in a patient.

### The Proof is in the Padding

Laboratory abnormalities are intriguing for scientists and alarming for clinicians but they are likely to be bewildering to people on HIV treatment. It's often the changes in the way they look in the mirror that matters foremost. Several studies are now starting to connect the dots by evaluating changes in fat deposits under the skin over time. For fat losses in the arms and legs, a technique called DEXA is reliable and well accepted. For increases in fat around the organs, a CT scan is a more acceptable — and more expensive — method. For fat loss in the face, patient self-evaluation or photography of facial fat wasting tell the story, but these, unfortunately, do not carry the same weight as more objective readings such as DEXA.

**Some people still have fat and happy cheeks after years on d4T. If their viral load is suppressed and they tolerate their drugs they'll probably see no reason to switch.**

The report that's gotten everyone's attention comes from a large trial that compared nelfinavir to efavirenz at the same time it compared AZT/3TC with d4T/ddI in people starting their first ART regimen. The trial, called ACTG 384, was conducted by the federally funded AIDS Clinical Trials Group. Results were first presented in July, 2002 in Barcelona and an additional analysis of fat loss was presented at the Lipodystrophy Workshop.

The fat loss substudy of ACTG 384, (ACTG 5005s) measured subcutaneous fat by DEXA in the arms and legs of 157 volunteers at baseline. The results from comparisons at weeks 48, 64 and 80 were presented. Overall, people in both the AZT/3TC group and the d4T/ddI group experienced a brief increase in subcutaneous fat during the first weeks after starting treatment. This may be due to a general improvement in constitutional health that follows the initial suppression of viral load. But by week 48, the average amount of subcutaneous fat in the arms and legs had declined by 7.5 percent in those on d4T/ddI, and was starting to drop, but still above baseline, in those on AZT/3TC. By week 80, the d4T/ddI group was down about 15 percent on average, while the AZT/3TC had slipped by about 7 percent.

When the same group was analyzed by whether they were on nelfinavir or efavirenz, not surprisingly, a greater loss of limb fat was associated with being on the protease inhibitor. At week 80, those on nelfinavir plus nukes were down by 18 percent, while those on efavirenz had sustained a 10 percent fat loss on average. A breakout of results by individual three-drug combinations was not shown and the role of d4T relative to ddI in causing fat wasting cannot be determined from this data.

The TARHEEL study that looked at lactates also measured changes in subcutaneous fat by DEXA after the switch was made from d4T. Of the 118 people with lipodystrophy who enrolled, over 80 percent had been on d4T for over two years. Three-quarters of the volunteers switched to abacavir and the rest to AZT. At 48 weeks, the biggest improvement was noted in the arms, with those on abacavir experiencing an average 37 percent increase in subcutaneous fat and those on AZT a 17 percent gain. Fat gains to the legs were less profound, with abacavir associated with a 15 percent average increase and AZT with about half that. However, a comparison of CT scans of visceral fat at baseline and at 48 weeks did not show a significant change. As with the lactate data, this is a before-and-after study with no concurrent control, and other factors may have played a role in these effects. Yet with the weight of evidence now implicating d4T in accelerated subcutaneous fat loss, when is reasonable doubt overruled by unreasonable risk?

### Do You Feel Lucky?

It's likely that all of the nucleoside analogs contribute to mitochondrial toxicity — some in some cells more than others; some sooner than others. But d4T seems to offer a fast track to fat wasting for far too many people who start taking it. Of course, not everyone is affected — that's the quandary. Some people still have fat and happy cheeks after years on d4T. If their viral load is suppressed and they tolerate their drugs they'll probably see no reason to switch. But people choosing a regimen today have a different decision to face — and there's no way to predict how things will go. If Zerit accelerates fat wasting, then there may be better first choices for a nucleoside analog.

Many people on treatment and their doctors pronounced Zerit guilty long ago. The next hearing should come when the committee that writes the federal treatment guidelines meets again to redraw their recommendations.

# My New Liver

*By Larry Kramer*

It is very, *very* hard to obtain an organ transplant in the United States. First, there are so few organs available. Second, it is hard to locate a transplant center willing to do coinfecteds — that's what they call you when you have a virus like HIV with hep B or C. Third, if and when they accept you, you have to wait in line. Depending on which part of the country you are applying from, and which medical center, it takes varying amounts of waiting time. It never happens quickly. There is far too much red tape and bureaucracy for that. Fourth, and perhaps first, you have to do an awful lot of investigation, research, phoning, faxing, e-mailing, pestering, even (how shall I put it?) raising your voice (politely, of course) to accomplish any of this. Patient empowerment takes on new meaning. You have to become a very fervent activist, for yourself. If you aren't feeling so hot then you need someone with persistent and unflagging energy to do it for you. You need such a person even if you are feeling great. A transplant is something you simply cannot enter into on your own. In fact, no transplant center will accept you if you cannot show that your support system is visible and strong.

But if you know you are going to die if you don't get a new organ, as was my case, you'd be surprised what a motivation this can be. I was given six months and was down to the wire when I finally got the call. At 67 I am the oldest person thus far transplanted with a new liver. My surgeon says in all seriousness that you are as old as your liver. I now have the liver of a 45-year-old man. Each day I feel vital and vibrant. I have no side effects. My hepatitis B appears to be gone from my body. And I truly feel like I am 45 again. Everything I went through was worth it, tremendously so.

You must investigate the half-dozen or so medical centers (the number is growing) that will take us. You must never stop your efforts to a) make a transplant surgeon evaluate you and b) get one to accept you. Many people apply to several different centers, but that can be very expensive. There are a lot of evaluation testing costs you must bear before you can be officially accepted, and your insurance, if you have any, picks these up only if and when you are accepted for transplant. I was lucky. There happened to be a spurt of interest in transplanting coinfecteds when I applied. It helps to be a scientific curiosity. I believe I was the 22nd coinfected to be transplanted. The NIH is currently preparing a research protocol to study transplants for coinfecteds; one of these days it will be approved and you might qualify for that.

When you finally find someone willing to accept you, you have to figure out how to pay for your transplant. No medical center will take you unless you can prove up front that you can pay. Not long ago if you were coinfected and looking for a new liver, you would have been turned down by your insurance company because saving your life was considered experimental. That's changed because of heroic surgeons like John Fung at the University of Pittsburgh Medical Center who knew better and proved it and confronted the insurers himself. Still, insurance companies usually have to be challenged if they turn you down, which on the first go-round they usually always automatically do, hoping you will not appeal. Medicare rejected me the first time but we appealed and in one day they had reversed their decision. Empire Blue Cross, my secondary insurer, accepted me immediately.

**A transplant is something you simply cannot enter into on your own. In fact, no transplant center will accept you if you cannot show that your support system is visible and strong.**

My liver transplant has cost Medicare, so far, over $500,000 and Empire Blue Cross, so far, over $100,000 for the continuing medications I must take, including a monthly pop of some $10,000 for something called Hepatitis B Immune Globulin, which I believe I must receive for the rest of my life. And you need to get your blood tested every few weeks. That costs a lot too.

So we are not talking about an easy or inexpensive ride here. The easiest part, believe it or not, was the transplant itself. I wasn't in any pain, ever. The recuperation period is long; getting your wind and motor abilities back can require many months of physical rehab and taking it easy. You must have patience, which I don't. Months of not doing anything can verge on the depressing. And if you don't live near a transplant center, you may have to move close by for the months of the whole process. My lover and care partner (two different people, and I couldn't have got through the process without either one of them) lived with me in Pittsburgh for many months. I needed the love of my partner, David Webster, every single minute. Boy did I need it. This is lonely and cosmically metaphysical stuff to live through. (One day they tell you you're going to die, and then suddenly you don't.) Hugs and kisses and smiles and homemade food and constant gentle urgings that

"you can do it" sure help you get better faster. And I was not an easy patient. I know that. And I needed the bossy efficiency of my very own Nurse Ratchett, Rodger McFarlane, who had every secretary, nurse, technician, and doctor at Presbyterian Hospital extra-attentive to his patient's case.

I was additionally lucky because I was able to meet the criteria for acceptance last year. I don't think I would have qualified under new guidelines, called MELD (Model for End Stage Liver Disease), which came into effect at the beginning of this year. The guidelines were developed by the Mayo Clinic, and consciously or unconsciously, MELD criteria appear to be blatantly discriminatory against coinfecteds. As I understand them, and very little about the current or past organ allocation system is understandable (even by the doctors who get the organs), the abnormal blood markers they look for to be considered for acceptance are not ones that people with HIV typically have out of whack. For instance, my PTT, bilirubin, and creatinine were not greatly elevated. But I was still dying and my liver was still conking out. Yes, you say "go figure" a lot in this whole process. And figure you do... or else you die.

Alas, most people in need of new organs don't make it. My memory is filled with haunting images of desperately sick people in the UPMC clinic waiting room hoping for a chance to grab an arriving surgeon's arm and literally beg him or her for a liver. And of the stories of uninsured recipients telling me how everyone in their entire family or indeed community or indeed town had sold everything they could to pay for their chance at life.

It shouldn't be like this, of course. We know all that. It is not right to have a system that excludes most of the people who desperately need its services. Yes, I know that I have been very, *very* lucky. I can shout "Persistence!" to the world but all activists have learned the hard way: we don't get anything without a terrible fight. If we want to live, we must fight like hell. And the fighting must never stop.

*Larry Kramer co-founded Gay Men's Health Crisis and founded ACT UP.*

# Botswana's High-Stakes Assault on AIDS

*By Roman Rollnick*
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*www.africarecovery.org*

The gleaming floors, white-frocked technicians and humming electronic equipment of the Botswana-Harvard HIV Reference Laboratory here in Gaborone, Botswana's capital, are distant in more ways than geography from the dusty villages and crowded mining compounds on the frontline of Botswana's desperate struggle against HIV/AIDS. But closing the gap between the resources available at this modern new facility, and the nearly 40 per cent of the adult population infected with the deadly virus, is at the heart of Botswana's high-stakes effort to provide comprehensive HIV/AIDS treatment to all of its citizens. In January, Botswana became the first country in Africa to offer expensive, but life-saving, antiretroviral drugs (ARVs) and other medications to all who need them through the public health system.

It is a costly and ambitious undertaking, one that many health care experts say cannot be done in Africa. But for the 330,000 Botswanan adults estimated to be HIV-positive, access to ARVs and to ongoing care, counseling and testing, is a matter of life or death. The vast but sparsely-populated territory has the highest HIV infection rate in the world. Some 26,000 people in this country of less than 1.6 million died from AIDS-related illnesses last year alone. "We are threatened with extinction," President Festus Mogae told the UN General Assembly last year. "People are dying in chillingly high numbers. It is a crisis of the first magnitude."

More than Botswanan lives may be at stake, however. For years, some international health experts, backed by many donor governments and agencies and the powerful pharmaceutical industry, have argued that poverty and the absence of infrastructure make it impossible to successfully treat large numbers of HIV-positive people in developing countries with AIDS med-

ications. Rather than waste resources on a failed effort to treat those already ill, they assert, scarce funds should be spent preventing new infections through education and prevention programs.

Activists counter that pilot projects have demonstrated the feasibility of treatment programs in developing countries, and that only a combination of treatment and prevention can turn the tide against the disease. Many advocates charge that opposition to large-scale treatment programs is fueled more by concerns for patent rights and profits than genuine doubts about practicability.

Botswana is the first African test case. Success in treating large numbers of patients will buttress the argument for greatly expanded treatment efforts in the rest of Africa and other developing regions. Failure will badly undermine the call for greater treatment access for the world's poor. Although the Joint UN Program on HIV/AIDS (UNAIDS) has long maintained that both prevention and treatment are necessary in the campaign against AIDS, fewer than 30,000 of the almost 29 million Africans infected with the virus have access to the ARV drugs that have dramatically reduced death rates in rich countries.

### Slow but Steady Progress

If any country in sub-Saharan Africa can implement a comprehensive HIV/AIDS prevention care and treatment program, observers say, it is Botswana. Unlike many of its neighbors, the country has enjoyed an unbroken period of peace and comparative prosperity since independence in 1966. Its government is widely regarded as among the most efficient and capable on the continent, and its annual per capita income of $3,300 is among the highest.

Still, the obstacles are formidable. Many Botswanans are migrant workers, employed in neighboring South Africa for much of the year, but maintaining farms and families back home. Migrants are at particular risk of infection because of the increased likelihood of contact with prostitutes and other casual sex partners while away from home. Often unaware that they have become HIV-positive, and unwilling to seek out testing and counseling because of the stigma associated with the disease, migrants are thought to be an important factor in the spread of the virus.

For those who do seek medical help, there is the problem of locating it. For HIV patients outside the private sector, there are only two government referral hospitals, one in Gaborone and another in the north, in Francistown. There are two smaller district hospitals in the country, but most public health care is delivered through local clinics offering only basic services.

The National AIDS Coordinating Agency (NACA) formally embarked on the national treatment program in January of 2002. Dr. Banu Khan, NACA's national AIDS coordinator, explained that the government set a target of 19,000 people for enrollment in their first year of ARV treatment under a $27.5M program in which people who require the drugs will get them for life. The ministry of health has calculated the cost of medications, testing and counseling at about $600 per person, per year. Over the first five years of the program, the Gates Foundation will provide $50M to help Botswana strengthen its primary health care system, while the giant U.S. drug manufacturer Merck will match that contribution with anti-retroviral medicines. The other half of the cost, some $100M, will be met by the government.

"As of June this year, we had an estimated 1,000 people enrolled," Dr. Khan noted. "We have 500 undergoing the treatment, while the remainder are still being screened to ascertain their precise treatment requirements." She termed that number "disappointingly" low, but said that more people are steadily coming forward. NACA says the volunteer patients include a "good mix" of educated and poorer rural people, some from the remote regions of the arid Kalahari in the west and northwest of the country.

Significantly, NACA officials say, initial indications are that very few patients have difficulty adhering to the complex ARV drug treatment regimes. The ability of poor and poorly educated patients to stick to strict medication schedules over a lifetime has been a major concern of health specialists and is an important aspect of Botswana's treatment initiative. Like Alcoholics Anonymous, NACA operates a "buddy system" whereby each patient is encouraged to form a special bond with someone close, who makes sure they remain on their medication schedule. The patients, in turn, counsel others who feel they may need help to come forward.

### Enrolling Mothers

Enrolling women in the program is a key priority because they make up more than half of all infected adults. Dr. Khan said that NACA is especially concerned at the low intake of mothers in a program intended to cut mother-to-child transmission of the HIV virus and keep infected mothers alive. Since the pilot project began, she said, only 2,000 women are currently undergoing treatment for AIDS-related illnesses. "We only opened up pilot sites two years ago. The

percentage of mothers enrolled, however, is not desirable. It is low and must be increased. We have problems here, especially the one of stigma." Health officials said enrollment by pregnant mothers had only been in the 11–20 percent range.

"Another problem is the status of women in relation to men," Dr. Khan added. Many women lack the power to control decisions about sexuality and remain under the authority of husbands, parents and in-laws all their lives. "How do you test someone if they do not get permission?" Dr. Khan asked.

**Many women lack the power to control decisions about sexuality and remain under the authority of husbands, parents and in-laws all their lives.**

"Then, with those who do enroll, they go home to a remote village with formula milk for their baby and are branded as suspect because they are not breast-feeding.... Mothers also worry about who will look after their baby if they die. But ARV therapy is now available in Botswana for these mothers and their babies, and I am hoping [enrollment] will increase now."

The country currently has 16 voluntary counseling and testing centers specifically for mothers—one in every district. These are stand-alone centers where one can discuss medical problems in privacy. "In the latter part of last year, we had a conference for people living with HIV/AIDS and it drew 500 people," Dr. Khan noted. "They went back to their homes and formed support groups to reduce stigma."

Dr. Khan said that NACA urgently needs more trained staff. "We have found that if you have a trained nurse dealing with many people in a rural clinic, for example, she does not have the time to counsel every HIV patient. So we are building a system of lay counselors, like social workers. For this, we do not necessarily need nurses and we have a program to employ 500 such lay counselors. We are hoping they will also play a key role in reducing stigma."

She said that people living with AIDS, both from the educated urban classes and rural communities, are increasingly aware that the government is providing free lifelong treatment. "These people are with us on a voluntary basis. No one is coerced. We counsel them on positive living, about prevention, about the importance of remaining on the treatment even if they feel better. And they usually go home and spread this positive message."

### *Staff Shortages Severe*

At present, NACA employs 10 doctors working full time on HIV/AIDS at the Princess Marina Hospital in Gaborone, and five at each of the other hospitals. Patients are also seen at the smaller health facilities, some of them mobile clinics, around the country. Uniquely for an African country, NACA says, almost no one is more than 8 km away from a clinic where they can seek medical help. Even in the remotest areas of the Kalahari, most people are just 15 km away. These clinics decide what sort of treatment people need, and either refer them to a hospital or provide them with ambulance transport if required.

Ms. Catherine Sozi, a British-trained Ugandan doctor based at the UNAIDS office in Pretoria, South Africa, said Botswana can sustain its national health scheme for AIDS patients even though the drugs are required for life. "However, there is an acute, absolute shortage of doctors, nurses and counselors in Botswana's health care system," she said, citing a recent UNAIDS assessment. "Although we did not have time to calculate the number of extra health workers needed for the ARV program, the numbers are substantial. If a first recruitment for ARV treatment would cost one hour of a doctor's time, recruiting 10,000 new patients in three months, for example, would require at least 20 full-time doctors doing nothing else but supervising these patients."

The shortage of doctors, pharmacists, nurses and counselors is compounded by the fact that over 90 percent of doctors in Botswana are foreigners who do not speak Setswana. Counselors too are recruited from abroad and need to spend time becoming familiar with the local culture. Many spend only a brief period in the country, thus exacerbating the need for frequent training and supervision to ensure proper medical care. There also is concern that many nurses, once trained and registered, emigrate to better-paid jobs abroad.

The government is seeking to recruit up to 200 new doctors from South Africa, Cuba and other nations to administer the drug program. "In return for their travel and accommodation expenses, many are coming to give their time free of charge," Dr. Khan explained. "They know the government is serious in addressing this epidemic."

The shortage of pharmacists outside the major hospitals is another problem. UNAIDS found that Botswana's few pharmacy technicians already have to manage drug supplies and distribution in the hospital and surrounding clinics. "They need support if they are to handle sensitive drugs like ARVs," Dr. Sozi said. Because Botswana will have to rely for some years to come on foreign health professionals, she noted, UNAIDS is recommending appropriate courses for them about local culture, health

policies and protocols. Many current staff will require crash courses on ARV treatment issues.

Testing, monitoring and surveillance of the Botswana AIDS plague, as many now call it, is carried out by the new Botswana-Harvard laboratory at the Princess Marina Hospital. The first of its kind anywhere in Africa, the laboratory, with a staff of 50, is equipped with gene sequencers and blood cell sorters, enabling scientists to keep track of the spread of HIV, especially the HIV-1C strain prevalent in this part of Africa.

### *Combining Treatment and Prevention*

Botswana is supporting the new drug treatment policy with an expanded and more aggressive education campaign, modeled in part after Uganda, which has successfully reduced new HIV infections through sustained public education. President Mogae is determined to make sure that the message of free treatment gets out —through radio, billboard campaigns and by word of mouth.

Mr. Edmund Dladla, national coordinator of the Botswana Network of People Living With HIV/AIDS, welcomed the president's leadership. "Any person who is of working age, who has a job and some education talks about it. And everyone wonders about the impact AIDS is having, not only on those close to them, but also on the country as a whole. People are scared."

"For a decade," he continued, "until the end of the 1990s, we were in a state of denial, blaming the crisis on foreigners. Then, as we realized its extent, we started acting. Today, I would say the government is very transparent, pro-active and accountable. We are the most advanced African nation in this struggle—and believe me, I would not have said that just three years ago."

### *Employers Get Involved*

Botswana's private sector has also become involved. Three years ago, the country's biggest employer, the Debswana diamond mining company, realized after testing its 6,000-strong workforce that fully a third of workers aged between 24 and 40 were HIV-positive. With revenues of some $1.8B dollars a year, and skilled miners scarce, the company set up its own HIV/AIDS scheme.

"We realized we had to do something fast because diamonds are the foundation of our economy," said Ms. Tsetsele Fantan, director of the company's program. She said Debswana agreed to provide free treatment for each infected employee and one legal spouse, while the government would provide treatment for other partners and their children. The government has also urged major banks, transport companies and even petrol stations to provide better levels of health care and make HIV counseling and treatment available to their employees.

**Botswana is supporting the new drug treatment policy with an expanded and more aggressive education campaign.**

"This collaborative program is designed to demonstrate the benefits of a comprehensive, multi-sectoral approach to improving the care of people living with HIV in a country with limited resources," said Dr. Clement Chela, of the Botswana Comprehensive HIV/AIDS Partnership. The fact that ARVs are now freely available, he added, has become a motivating factor for people to come forward. "The program we have put in place here can work in other countries in Africa, and with international financial help, it can be sustained."

# Drug Fact Sheet Review

At the Barcelona AIDS Conference, an international network of treatment advocates met to begin laying groundwork for a treatment preparedness project for resource-poor settings. The goal of treatment preparedness is to increase awareness of the promise and realities of antiretroviral therapy in anticipation of their availability and to educate and mobilize well-informed local advocates. A preliminary stage of this project has begun to collect and evaluate existing educational materials that can be used as written, or as a model for locally produced materials. Several sources of drug fact sheets and treatment information resources are reviewed here.

*Methods:* An Internet search was made during the week of September 16, 2002, to identify HIV drug fact sheets and other HIV drug information resources. Information about the nucleoside analog 3TC (Epivir, lamivudine) was selected and copied into a text document. This material was evaluated for its discussion of the drug's action and of its side effects. The texts were graded on the criteria of accuracy, currency and clarity. The reading level of each resource's entire 3TC entry was assessed using the Flesch-Kincaid Reading Level utility internal to Microsoft Word. After the specific sections were evaluated, each criterion was graded and an overall score was assigned. Finally, a brief assessment of the source's additional resources was noted.

*Results:* Treatment information resources available on the Internet can be divided into two categories based on the mode used to address the reader, on the format used to discuss serious side effects and upon the Flesch-Kincaid reading level.

*Simple Fact Sheets:* Simple language fact sheets tend to address the reader directly, i.e., "You should know..." Simple fact sheets also tend to list the most common side effects before warning about rare potential adverse events. The reading level of simple fact sheets ranged from 7.4 to 10.0. These fact sheets are designed to be used by clients who may be learning about HIV treatment for the first time.

*Treatment Information Resources:* Treatment information resources tend to discuss information objectively and reference clinical trial evidence. Serious side effects are usually listed first as is typical of information presented to health care professionals. Reading levels are at the top end of the scale (11.0–12.0) These resources can be used by educated or motivated readers, or as a "wholesale" source of information that is ultimately retailed to clients through treatment educators.

## *Simple Fact Sheets*

✙ ✙ ✙
Treatment Information in Asian Languages
Asian Community AIDS Services (ACAS)
Ontario HIV Treatment Network
www.acas.org
Last updated: July 2001
Languages: Vietnamese, Chinese, Tagalog, English;
Formats: PDF, English text available online
Reading Level: 7.6

ACAS offers a charming fact sheet, if that is possible. The lightness of language and clarity of ideas is refreshing. The notion that HIV drugs can "help you get your health back" is touching and true—a message not seen elsewhere. The clear descriptions of the types of blood cell deficiencies may not be necessary, but they are edifying. There are a few awkward grammatical passages in the English version that could have been smoothed by a proofreader. I'm told the Chinese translation is formal but clear on the facts.

The tone of this material is non-judgmental and unfailingly polite: "3TC does not kill the virus or cure AIDS. It also does not prevent the transmission of HIV, so please remember to always take precautions if you are having sex (e.g., use latex condoms) or using drugs (e.g., use clean syringes)."

The producers of these fact sheets seem comfortable with a harm minimization approach to treatment education, advising, for example, not to skip a dose just because you want to have a drink. But this fact sheet takes harm reduction a little further: "3TC liquid contains sugar, you should clean your teeth regularly after taking the medication to prevent tooth decay."

Treatment Information in Asian Languages is available as text or in a PDF format as a two-page handout. The design is simple and does not rely on graphics or color. This fact sheet is rivaled by New Mexico AIDS INFOnet for its simple reading-level score but runs about a third longer and packs in more concepts with grace. Top honors.

✙ ✙ 1/2
New Mexico AIDS InfoNET
www.aidsinfonet.org
Last updated: July 14, 2002
Languages: English, Spanish
Formats: PDF, Word, Text
Reading Level: 7.4

New Mexico AIDS InfoNET's fact sheets are very popular with educators for their simple language and consistent format. But one of the casualties of simple language is loss of precision and accuracy. There are occasional lapses into unexplained concepts here, such as genetic code, or the use of medical terms like hypertension instead of high blood pressure.

One problem with the freshness of InfoNET fact sheets is that they are widely distributed by third parties that may not have the latest version on line. For example, the 3TC fact sheet found on AIDS.org is dated February 7, 2002, and lacks news of the approval of once-a-day dosing found on the main InfoNET site.

The fact sheets are organized by category and reference related fact sheets by number. However, the web site itself is cluttered and it can sometimes be difficult to locate what you want. All of AIDS InfoNET's many fact sheets are translated into Spanish and can be downloaded in a format ready for the Xerox machine.

✙ ✙
Positive Words
www.positivewords.com
Last Updated: 2001
Languages: English, Spanish
Formats: PDF, Simple Text, Online Text
Reading level: 9.5

This fact sheet manages to educate about broader concepts while informing about 3TC in particular. Readers are advised to tell their doctors about any street drugs used. They are also advised to space their dosing when taking 3TC with ddI. The "why" is given along with "dos" and "don'ts". This is a commercially sponsored site, however editorial independence is protected by a panel of community advisors.

Positive Words offers an abundance of brief, easy to read articles about a wide array of HIV-related topics. If you can manage to navigate the confusing site, you can find some basic drug fact sheets that balance readability with accuracy and brevity.

✙
JAG Enterprises
www.jag.on.ca/pdf/Antiretrovirals
Last Updated: October 2000
Languages: English, French, Spanish
Formats: PDF
Reading level: 10.0

JAG Enterprises in Ontario, Canada, produces a series of HIV informational pamphlets for patients. These pamphlets have a friendly yet professional tone with enough white space to minimize the intimidation factor. Yet there is a pervasive tone of authority that many users may find disrespectful. For example, women are simply told they must use birth control methods with no discussion of why.

The reading level is fairly high and terms such as inhibit, abdominal and gastrointestinal are not defined within the text. Certain medical terms, such as neutropenia and pancreatitis are explained. The materials were written by a pharmacist (which may explain the tone of authority) and the site is sponsored by several major pharmaceutical makers. The colorful, illustrated fact sheets are preformatted and ready to print. The drugs are pictured in color photographs and there are spaces provided to note a persons's dosage and contact phone numbers.

AIDSmeds.com
www.aidsmeds.com
Last updated: June 24, 2002
Languages: English
Formats: Online text
Reading level: 9.5

AIDSmeds.com is intended to be a patient-friendly place for people considering or already taking antiretroviral therapy. And for the most part the writing is accessible. But after reading the long list of cautions and warnings here, it would be a wonder if anyone actually had the nerve to get a prescription filled. This is the place to go if you need to find out how to deal with a 3TC overdose (seek emergency medical attention). There is a clear presumption that the reader has unlimited access to medical advice; readers are advised to consult their doctors no less than twenty times on one page. Mixed in with all the cautions is the odd suggestion that, "Lamivudine may also be used for purposes other than those listed in this medication guide." Cake decorations?

It was interesting to compare the 3TC entry to that for a more recently approved drug, tenofovir. The writing style and format is completely different and the obsessive warnings are mostly absent. For the newer drug, efficacy is discussed and the evidence is referenced. Despite some spelling errors, it delivers a far more useful plate of information. This is a commercial site and affects an active magazine-like design that is visually busy and sometimes overwhelming. AIDSmeds.com is a great resource for someone with time to browse everything that is offered and has a 24-hour hotline to a physician.

AIDS Treatment Data Network (ATDN)
www.atdn.org
Last updated: August 22, 2002
Languages: English, Spanish
Formats: Online text
Reading level: 11.5

Older fact sheets often retain artifacts of when they were first written —when combination antiretroviral therapy was still new: "Many studies have now shown that using lamivudine in combination with at least two other anti-HIV drugs can prevent the virus from getting resistant." The benefits of combination therapy may now be considered dogma; it's better to simply stress the importance of using at least three meds together on a consistent basis; no combination in itself can prevent resistance. The dated tone and inaccuracies aside, grammatical errors, spelling errors and typographical errors will erode a reader's confidence in this material. It's time for a rewrite.

HIV Nordic Net
www.nordicnet.org
Last updated: 2000
Languages: Danish, English, Finnish, Icelandic, Norwegian, Swedish
Formats: Online text
Reading level: 12.0

This material seems to have been translated into English and suffers from frequent awkward Nordic sentence structure: "...a real need to be aware of what they are is important for you to know." There seems to be a tautology in saying the drug "is normally very well tolerated by most patients who experience little or no side effects." It's the ones with lots of side effects that have trouble with tolerability. This material is rated at a high literacy level—for no reason other than the awkwardness of the writing.

GMHC Fact Sheet
Gay Men's Health Crisis
www.gmhc.org
Last updated: May 2000
Languages: English, Spanish
Formats: Online text, paper copies
Reading level: 10.3

GMHC does not currently offer a fact sheet for 3TC. For the purposes of this review, a fact sheet for Viramune was substituted.

These fact sheets are written in a conversational style, but that does not mean they are simple to read and understand. The discussion of side effects is poorly organized, with the risk of rash mentioned first, followed by common, mild effects, then back to liver side effects, which can also be life threatening—a fact not made clear here. The statement, "Viramune...has been known to cause hepatitis..." could easily cause confusion: does Viramune cause hepatitis C? For a drug with potentially far more serious toxicities than 3TC, this lack of clarity is unacceptable. GMHC says a new series of fact sheets is due out soon.

Project Inform
www.projectinform.org
Last updated: July 1997
Formats: PDF, Online text
Languages: English, Spanish
Reading level: 11.7

The material on this site is so old it would be laughable if not for the potential to mislead innocent readers: "... a number of ongoing studies are evaluating triple drug combinations which utilize AZT, 3TC and protease inhibitors (notably indinavir, also known as Crixivan)." Other reports of "ongoing" studies about double nucleosides are alarming. Warnings about lactic acidosis are absent. Accurate for the time when they were written, but not now, these fact sheets belong in a time capsule. They should be taken down until they are rewritten.

## Treatment Information Resources

✙ ✙ ✙
AIDSmap
www.aidsmap.com
Last updated: July 29, 2002
Languages: English
Formats: Online text
Reading level: 11.0

AIDSmap is a bright light in this constellation of treatment information. It begins with one of the better simple-language explanations of what 3TC does. In addition to listing the usual side effects, AIDSmap gives some advice for how they can be minimized, when they will be worst, and who might have more trouble than others. All efficacy statements are evidence-based and referenced. The site is up-to-the-minute and was the only one reviewed to include a report on the ACTG 384 study presented at the Barcelona International Conference in July. Medical jargon is usually explained in parenthesis, although occasionally terms such as "resistance" are introduced without definition. Overall, the reading level is higher than one would like for a simple fact sheet and the voice sometimes swings between direct address and third-person.

AIDSmap is unique in that it is scalable: the overview can expand into a review of virtually every clinical trial result ever published. Users of this site can go as deep as they like into what is known about 3TC. The site is also optimized for international treatment preparedness workers with the trade names of Indian generic versions of 3TC (Lamivir) listed along with Glaxo's. Best of the bunch.

✙ ✙
amfAR Global Link
www.amfar.org
Last updated: June 2002
Languages: English
Formats: Online text
Reading level: 12.0

This material is not intended for "retail" treatment education but gives a capsule review of all the salient points that a medical professional would want to know about 3TC. Safety issues are highlighted and key references are provided. Although the material has been recently updated and includes results of a tiny study of once-daily dosing, the important results from ACTG 384, presented in Barcelona in July, have not yet been added. Global Link should be useful to creators of treatment education materials as a source of reliable facts. Anyone who'd like to improve their knowledge of HIV treatment, complications and infections can find a wealth of information at Global Link. Hours of good browsing here.

✙✙
AIDS Clinical Trial Information Service (ACTIS)
U.S. Dept. of Health and Human Services
http://www.actis.org
1-800-TRIALS-A
Last updated: July 17, 2002
Languages: English, Spanish
Formats: Online text, telephone
Reading Levels:
Technical View: 12.0
Non-technical View : 11.5

Technical View

Fact sheets for PhDs. A scholarly review of what is known about 3TC right down to the drug's molecular weight and melting point (160°–162° C). Absorb this information and write your own fact sheet.

Non-Technical View

ACTIS (thankfully) boils down all the information contained in the Technical View into a simple one-page summary.

Although this is the non-technical version, the 3TC summary is written at a relatively high reading level, with many clauses and semicolons lengthening the sentences. Side effects are clearly described without jargon, and the less serious effects are put in context of when they are likely to occur. The term enzyme is defined but not necessarily in a way that will be meaningful for understanding its role HIV replication. The discussion of side effects makes the useful point that drugs have effects on the body—some desirable, some not. It may be that the cost of maintaining accuracy and clarity is the loss of simplicity. Overall, a great source of reliable information.

# Global Treatment Update

*By Bob Huff*

### *Global Fund Slow to Take Off*

The Global Fund for TB, Malaria and HIV has said that despite approving a first-round of initiatives in the spring worth $1.6B, no money has yet been disbursed. A second wave of funding requests, currently being evaluated, and subsequent waves, may push commitments to over $8B within the next two years (UN Secretary Kofi Annan estimates the need is $10B a year). Yet it's not clear at this point if the Fund will even have the cash to meet its initial check run. As of September, the Fund had only $500M in the bank to give out. Despite having received pledges of over $2B from world governments, there is a large gap between what has been promised and what has

## *Short Course* *Notes on HIV drugs in development*

**Pro-Drug Lobby**

Glaxo presented data on their "908" drug (formerly VX175) a version of Agenerase with a better pill burden and much improved tolerability. The trial compared 908 to nelfinavir, both in a twice-a-day regimen with abacavir and 3TC. At 24 weeks, drops in RNA and gains in CD4 counts were similar. If starting with viral load under 100,000, there was a similar likelihood of achieving VL under 400 copies. Glaxo's drug showed it's modest potency edge in those who started with VL above 100,000 at baseline. Your mileage may vary.

As expected, there was three times as much diarrhea on the nelfinavir arm. Triglycerides were lower on 908, an advantage that will likely go out the window if Glaxo shoots for once-a-day boosting with ritonavir. One note: the incidence of abacavir-associated drug allergy in this study ran between 5 and 8 percent, similar to the rate in the TARHEEL study—both higher than the 3 percent rate that Glaxo often quotes. Two other Phase III trials of once-a-day 908 plus ritonavir are underway. Data could go to the FDA next year.

**Fresh Air**

In his presentation of tenofovir data during a late breaker session at ICAAC, Joel Gallant of Johns Hopkins University prefaced his talk with a verbal disclosure of his relationships with various pharmaceutical companies. This was a first in my experience; it seemed to cause Dr. Gallant no pain, no one walked out, and the ceiling of the conference center did not collapse. His public disclosure put his cards on the table and allowed the data to be evaluated in the open air. Gallant's breakthrough should become the model for all presenters of clinical trial data.

**Onward T-20**

The FDA announced they have given T-20 priority review status for approval, which means they must say yea-or-nay by March 16, 2003—although the agency could act sooner. T-20 sponsor Roche is happy about this, but a persisting problem with drug production has them downplaying expectations about actually being able to deliver the drug to everyone who'll need it. Roche has scheduled a meeting with community members next month to discuss this issue, its expanded access program, and rumors of "golf-ball-sized nodules" at the site of injection. Physicians are returning from Roche training sessions buzzing about the importance of learning proper T-20 preparation and injection techniques. Not a bad idea.

**Atazanavir Update**

At ICAAC, Kathleen Squires presented 48-week data on Bristol Myers Squibb's low-tox PI hopeful, atazanavir (ATV). BMS 038 compared ATV head-to-head with efavirenz, both once a day, each backed up with standard BID Combivir. Both drugs turned in respectable efficacy results, each bringing similar proportions of the 810 treatment naïve participants below 400 copies, although only about half as many went below 50 copies. Resistance to ATV was uncommon, and a tantalizing suggestion was floated that ATV resistance, when it does occur, may possibly increase susceptibility to other PIs.

The great promise of atazanavir is that lipid abnormalities, which have been the bane of other PIs, seem to be absent with this drug. Triglycerides were somewhat elevated in the efavirenz group but actually went down for those on ATV. But this PI has one peculiar trait that will bear watching—elevated levels of unconjugated bilirubin are associated with ATV and produced 21 cases of jaundice in this trial. If this turns out to be a significant problem with TAZ, unkind consumers could take to calling it The Yellow Peril.

This large, worldwide study enrolled people into one of the broadest cross-sections of the world epidemic yet studied in a drug company trial and the demographics are notable. Over one third of the participants were women and about two-thirds were non-white. Hopefully, this kind of representation will reflect a trend in Phase III clinical trials to come.

been deposited in the Fund's account. Furthermore, money that is available to be disbursed has been held up as the Fund establishes procedures to route the money and provide accountability. News reports have said the Fund is still struggling to get on its feet operationally and even lacks working voice mail on its telephone system. Still, requests for funding continue to stream in.

On a positive note, the Fund has finally given guidance to grantees over the issue of generic medications. Bucking intense pressure from the pharma lobby, grantees now have a green light to seek drugs at "the lowest price possible," whether generic or branded.

### Excerpt from a speech by Stephen Lewis

*The Center for Strategic and International Studies —Washington, D.C., October 4, 2002*

I'm no optimist about the virus. But I simply don't believe, on the basis of personal observation, that we have to face Armageddon. In fact it enrages me the way in which we pile despair upon catastrophe, over and over again, rendering everyone paralyzed. You don't have to be some pathetic bleeding heart to see the potential strength in these societies at the grass roots, and know that if we could galvanize the governments, indigenous and external, and equip civil society, and address capacity and infrastructure with external resources, then we could defeat this pandemic. It is not beyond our competence.

I met not long ago with a thousand high school students in Addis Ababa, for a question and answer session that lasted an entire afternoon, and the intelligence and understanding and sophistication of those kids gives nothing but hope; I've met with the WFP truck drivers in Nazareth, south of Addis, as they tell their stories of the training they receive, and how they now always carry condoms on their routes; I've met at length with his Holiness, the Patriarch of the Ethiopian Orthodox church as we discussed how the UN family could set in process training for his 350 thousand priests so that they, in turn, could address their parishioners; I've sat over coffee with village women miles and miles from the Ethiopian capital, while neighbors gather to talk about how the virus is transmitted and how to protect themselves. They laugh self-consciously in the presence of a stranger, but they don't mince words.

I've attended the two day sensitivity sessions in Abuja, Nigeria, for the establishment of mother-to-child-transmission clinics—a tremendously impressive undertaking; I've sat with the doctors and nurses in a leading hospital in Benue state as they decide how they'll choose those who should receive anti-retroviral treatment when it begins, and how to handle the counseling; I've met with groups of People Living with Aids out in the Eastern region, near Onitsha, as the mothers talk about the kids they'll leave behind, and then make their eloquent, moving, unanswerable plea for treatment.

### Coke Announces Plan—Pressure to Continue

AIDS activists have been demanding that international Coca-Cola and it's local independent bottlers in Africa agree to pay for HIV treatment for all who need it among the 100,000 people employed to bottle and distribute Coke. On September 29, 2002, Coke, along with eight of the 40 bottlers they work with in Africa announced a plan to share the costs of AIDS treatment. According to a Coke statement: "The first bottlers to deploy the program are in Egypt, Morocco, Burundi, Congo, Democratic Republic of Congo, Reunion, Angola, Rwanda, Kenya, Tanzania, Ethiopia, Mozambique, Namibia, South Africa (some), Uganda, Botswana, Lesotho, Swaziland and Zambia. Given some of the infrastructure challenges, it will take up to 12 months to fully roll this out in these countries." The cost to Coke is estimated at about $5M per year.

Yet activists say this plan falls short on a number of counts. First, unless Coke presses holdout independent bottlers to join the plan, only a portion of Coke's workers will be covered. Second, the current plan will exclude children of Coke's workers. Finally, the plan intends to require a 10 percent co-payment to receive drugs. Activists fear that this amount—easily affordable by the company—may pose an insurmountable barrier for many low-pay workers.

GMHC treatment ISSUES

**Editor**
Bob Huff

**Art Director**
Adam Zachary Fredericks

**Volunteer Support Staff**
Edward Friedel

**Proofreaders**
Derreth Duncan
Edward Friedel
Richard Teller

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GMHC Treatment Issues
The Tisch Building
119 West 24 Street, New York, NY 10011
Fax: 212/367-1235
e-mail: ti@gmhc.org
www.gmhc.org

# We Must Have Presumed Consent

*By Larry Kramer*

More and more people with HIV and/or hepatitis B and/or hepatitis C are going to need organ transplants, particularly liver transplants. This is not an opinion. This is a fact. As more and more of us all over the world discover we are carrying one or more of these viruses, even if we are being treated for them—or particularly if we are being treated for them—the more likely it becomes that one of our organs is going to cease working effectively. And the longer we are being treated, i.e., the longer we live, the more that chance grows.



With all the new drugs for HIV and viral hepatitis, it is now safe—ok, kosher to transplant "coinfecteds," which is what people with viruses are called in the transplant world. The *New England Journal of Medicine* has even written approvingly of such procedures. Insurance companies can no longer simply refuse to pay for these hugely expensive procedures on the grounds that they are "experimental." These operations are no longer experimental. Too many of them have been done successfully.

Right now there are hundreds of thousands of people in this country waiting for organs. Most of them will die before they get them. Many of them will die after they have been put on a waiting list.

Why is this?

Because not enough people in America donate their organs to be used after they die.

It is as simple and as complicated at that. There are more than five people waiting for every organ made available by donation.

In many foreign countries this extreme shortage does not exist. That is because these countries (and they include Austria, Belgium, Denmark, Finland, France, Italy, Norway, Singapore, and Spain) have what is called a Presumed Consent organ collection system. That means that every person in that country is deemed to be an organ donor unless s/he specifically opts out. That means that when an accident occurs to a person who has not opted out, and brain death is declared, his or her organs can be taken immediately without the time-wasting rigmarole America requires for "approval." An organ only has a few hours to get from one body to the new one. In America you sign the back of your driver's license if you are willing to be a donor, and even then most centers still require permission from a family member, which, believe it or not, may not be given.

I have been trying, since my transplant, to find a way of changing America's organ donor system to one of Presumed Consent. Well, you would have thought that Presumed Consent was akin to the biggest blasphemy known to civilization. Opponents from the right, the conservatives, the orthodox, you name it, including, believe it or not, the ACLU (did you know that the dead had rights?) have screamed in opposition. These opponents do not care that Spain, a very Catholic country, has the best organ procurement system in the world.

And no one I can find knows how the system can be legally changed. Who does it? Congress, by passing a law? HHS, by issuing an edict? State by state or community by community, by putting it on a local ballot? As Robert Bazell, the chief medical correspondent for NBC Nightly News, warned me when I embarked upon this new activist journey, "Larry, you will find that it is like punching air."

The one person who can help change this system more than anyone else is Senator Bill Frist (R-TN). He is a transplant surgeon himself. He knows the hideous horrors of watching people desperate for organs die. But he is a politician, and a Republican, and from the South, so he is not exactly willing to be Mr. Flag Waver for organ transplants. He has prepared a bill, with Sen. Christopher Dodd (D-CT), to investigate Presumed Consent. But this bill has no hope in hell of getting passed, which is not so bad because it is such a wishy-washy, namby-pamby piece of stand-in-place legislation that we are better off without it.

AIDS activists have been here before. It is the beginning of a new crisis and no one of any importance wants to pay it an iota of attention. In the coming years the number of people around the world waiting for new organs is going to rise to the millions from the several hundred thousand currently in need. Once again I find myself screaming out loud about a huge and coming catastrophe and find that no one is listening.

I would like to close with some words from Dr. John Fung, who saved my life: "Patients are dying and the public still does not understand that saying no to donation means someone will die. No one wants to be so blunt—no one wants to raise the American conscience to make people feel that it is their human obligation to pass along their body to the living when they die. This is a systematic deficiency in American culture, the idea that you are out only for yourself and have little or no obligation to society as a whole."

*Tell Senator Bill Frist: America must have presumed consent!*

*Bill_Frist@frist.senate.gov or call: 202/224-3344*