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Glasgow Conference Adds to Treatment Controversies

by Gretchen Schmelz Armstrong

More than 2,500 experts gathered in November for Glasgow's biennial International Congress on Drug Therapy in HIV Infection. The conference setting imparted a European flavor to the proceedings, which tackled the ongoing themes of antiretroviral therapy — when to start therapy, how to start, pharmacology and drug toxicities. Metabolic side effects, in particular, garnered a renewed focus.

AZT or d4T? Is There Any Difference?

Scientists have known since 1994 that cells cultured outside the body convert AZT to triphosphorylated d4T-the medically active form of d4T with three phosphates attached. Cells convert AZT, d4T and all other nucleoside analogs to the drugs' biologically active triphosphate forms, but they ordinarily do not convert one drug to another.

Now, Jacques Grassi and his colleagues at the University Hospital of Bicêtre outside of Paris report that the same phenomenon occurs in the body. While perfecting a test to detect triphosphorylated d4T inside cells, the researchers found d4T in cell samples that they expected to test negative. These cells came from volunteers on AZT, not d4T. Grassi subsequently looked at cells from everyone taking AZT in his study and found d4T in every sample. d4T concentrations ranged from 3% to 37% of the concentrations of triphosphorylated AZT.

"We don't find any d4T in the blood," said Grassi. "It is an intracellular process. It is not reversible-people on d4T do not make AZT. That makes sense because chemically that would be very difficult. The concentration of triphosphorylated d4T is always lower than the total concentration of AZT. And also, it is very specific. We do not see this with people not on AZT or d4T therapy."

This discovery raises questions about how much triphosphorylated d4T contributes to AZT's efficacy and toxicity profile. Studies in recent years have implicated d4T as a major factor in peripheral fat loss (lipoatrophy) among people on anti-HIV therapy. d4T also is highly prone to cause such short-term side effects as neuropathy. AZT can

lead to reduced levels of red and white blood cells or muscle wasting. These toxicities may result from inhibition of the mitochondria, the cells' energy-producing units.

In addition, prior AZT seems to compromise d4T's effectiveness. Researchers have related this loss of anti-HIV activity to the emergence of drug-resistant HIV and/or decreasing cellular phosphorylation of AZT and d4T.

If there is d4T mixed with the AZT inside cells, either drug's overall effects on both the body and HIV might turn out to be similar. The question is fraught with commercial implications as well as medical ones.

Grassi speculates that so far, because the molecules are so different, it appears that most of AZT's side effects result from AZT itself. But the same may not be true for the few people who convert large amounts of AZT to d4T. "This is an important finding," concluded Grassi, "because this proves that by looking at intracellular metabolism we can see relevant things that may explain particular efficacy and toxicities."

New Protease Inhibitors versus Old

On the experimental drug front, Robert Murphy of Northwestern University in Chicago reported interim 12-week results from BMS AI424-044, a substudy of AI424-008. AI424-008 compared 400 mg or 600 mg atazanavir daily to nelfinavir 1,250 mg twice daily (both combined with d4T/3TC). At the end of the 48-week 008 study, the 69 people assigned to take nelfinavir could switch to the 400 mg atazanavir dose, and 63 did so. The intent of 044 was to observe the changes in blood lipids of those who switched. The substudy also compared the lipid changes with those of the participants who started on atazanavir in the 008 study.

Twelve weeks after switching from nelfinavir to atazanavir, patients' mean lipid levels dropped (total cholesterol, from 213 to 175 mg/dL; low-density lipoprotein cholesterol, from 138 to 104 mg/dL; and triglycerides from 156 to 108 mg/dL). As for adverse events, severe blood bilirubin elevations occurred in 23% of the 400 mg atazanavir group, 35% of the atazanavir 600 mg atazanavir group, and 10% of the group that switched to 400 mg atazanavir after 48 weeks on nelfinavir. High bilirubin levels are a sign of liver malfunction and can lead to jaundice.

In the latebreaker session, Dirk Schürmann of Charité University Hospital in Berlin shared 48-week results from the 660-person SOLO study. The trial tested a once-daily combination of 1,400 mg fosamprenavir (which the body breaks down into the protease inhibitor amprenavir) plus 200 mg ritonavir against a control consisting of 1,250 mg nelfinavir twice daily. Trial participants also took abacavir and 3TC twice daily.

At 48 weeks, 68% of people in the fosamprenavir/ritonavir arm and 65% of those in the nelfinavir arm suppressed viral load to below 400 copies/mL. According to Schürmann, this was a "noninferiority study." The trial was not designed to show that one treatment was better than the other, and the difference was not statistically significant.

Although more people experienced virologic failure on nelfinavir compared with those on fosamprenavir (15% versus 4%), more people on fosamprenavir prematurely discontinued the study compared with those on nelfinavir (25% versus 15%). The top three adverse events of at least moderate severity were diarrhea (9% versus 16% in the nelfinavir group), nausea (7% versus 5%) and vomiting (6% versus 4%). There was a jump in triglycerides in the fosamprenavir/ritonavir group, from 150 mg/dL at baseline to approximately 240 mg/dL at the end of 48 weeks. The mean increase was not as large in the nelfinavir group, where it increased from 150 mg/dL at baseline to 210 mg/dL in the same period.

Zeroing in on Lipodystrophy

These studies reflect the growing concern for diagnosing and ameliorating the alterations in lipid and sugar metabolism that occur during HIV therapy. These metabolic perturbations may heighten the risk of heart disease and diabetes. More dramatic are the visible changes in fat distribution — loss of fat below the skin and/or accumulation of fat deposits around the central organs. Clinicians still lack a precise way to measure or diagnose such "lipodystrophy."

A precise diagnostic definition of the lipodystrophy syndrome or syndromes is essential for several reasons, primarily for recording accurate adverse event data in clinical trials and for following patients receiving care. In addition, guidelines for treating lipodystrophy — and third-party payment for treatment — will depend on strict diagnostic criteria.

Conflicting descriptions have emerged from data from the HIV Lipodystrophy Case Definition Study and the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) Study, both of which were presented at Glasgow. "There have been moments in which the differences have become more highlighted than they ought to have been," said William Powderly of Washington University in St. Louis. Powderly was the only clinician who participated in

both studies. "I think it is more a reflection of the personalities involved than a truly scientific problem."

In the Case Definition Study led by Andrew Carr of St. Vincent's Hospital in Sydney, Australia, researchers recruited 417 HIV-positive people identified as having lipodystrophy by their doctors' and their own subjective assessment. The researchers additionally recruited 371 HIV-positive people who did not think that they had lipodystrophy, nor did their doctors. Carr then looked for differences between the two groups and came up with scoring system by which a physician could diagnose lipodystrophy with about 80% accuracy.

The factors involved in the lipodystrophy score were age, gender, HIV duration, HIV disease stage, waist-to-hip ratio, anion gap (a measure of blood electrolyte balance), high-density lipoprotein cholesterol, trunk-to-limb fat ratio, leg fat percent and visceral-to-subcutaneous abdominal fat ratio. Using trunk CT and DEXA scans to reveal adipose tissue patterns only slightly improved diagnostic accuracy.

In contrast to the Case Definition study, the FRAM investigators gave questionnaires about body image to both HIV-positive and -negative men. The survey was bi-directional, so participants could report if they noticed gain or loss in peripheral or visceral (central) fat. Trained investigators also independently evaluated the participants. Of the 357 HIV-positive men surveyed so far, 40% reported loss of peripheral fat, and many who reported peripheral fat loss also reported central fat loss. The chief FRAM investigator, Carl Grunfeld of the San Francisco Veterans Affairs Medical Center has concluded that although someone may experience peripheral fat loss and central fat gain, they are not statistically linked. In short, they are two separate syndromes.

"Carl [Grunfeld] is correct in that it does not appear when you look at a large cross-sectional study like FRAM that the two are necessarily linked," said Powderly, who attempted to put both presentations in context. "It is also true as Andrew [Carr] has pointed out that the two tend to occur together. It's unusual to see a patient who exclusively has one or the other. Where there has been some contention and controversy is that the case definition worked on the assumption that it was one syndrome. It didn't discriminate between those that gained or lost fat. It simply asked, 'Do you think you have lipodystrophy?' Now as it turned out, the majority of those involved in the case definition felt that they had done both. What Grunfeld's data suggest is that the two do not necessarily go hand in hand."

Powderly also stressed that prospective studies will offer a more accurate picture of the syndrome, or syndromes. "The one disadvantage of both of these studies is that they are one-time-only cross-sectional studies, and depending on when you look at the patient and the evolution of these changes, you may see one phenomenon being more prominent over the other. When in fact the data from the prospective studies suggest that these changes are occurring over time."

A Little Dab Will Do You

Radically new types of HIV therapy could help eliminate the lipodystrophy problem (unless it is somehow inherent in recovery from chronic HIV infection). Therapeutic vaccines are one alternative approach that is gaining interest. The concept is to first suppress HIV with antiviral drugs. Then as the immune system recovers, build up anti-HIV immunity by introducing some of the virus's proteins into the body. It is hoped that this induced immunity will ultimately allow patients to discontinue the drugs without experiencing HIV rebound.

At Glasgow, Julianna Lisziewicz of the Research Institute for Genetic and Human Therapy in Washington, DC reviewed DermaVir, a novel topical vaccine developed at her institute. DermaVir contains the DNA form of HIV genes mixed with dextrose, water and a special adjuvant. Rubbing DermaVir on the skin allows the Langerhans cells-dendritic cells of the skin-to absorb the foreign DNA and take it with them as they move into nearby lymph nodes. The vaccine DNA uses the Langerhans cells to make HIV proteins. Segments of these proteins appear on the cell membrane and activate CD4 and CD8 cell defenses that can kill cells infected with real HIV.

Lisziewicz described the results of two monkey studies that used DermaVir in conjunction with antiviral drugs to treat SIV, the monkey version of HIV. In the first study, ten macaques with high SIV viral loads and signs of AIDS were randomized to receive continuous or intermittent therapy. The monkeys receiving intermittent therapy experienced consistent viral rebounds during six successive treatment interruptions. Adding DermaVir to later treatment cycles suppressed viral rebounds from a median 4.3 million copies/mL to less than 200. In the second study, 14 chronically SIV-infected macaques without AIDS were randomized to receive intermittent therapy plus or minus DermaVir. Those on intermittent therapy alone also experienced virus rebounds during treatment interruptions similar to the monkeys with AIDS. The monkeys randomized to also receive DermaVir progressively suppressed viral

replication during treatment interruptions from a median 34,000 copies/mL to less than 200. In both studies, decreased viral load rebound correlated with heightened anti-SIV responses by CD4 and CD8 cells.

ACTG A5176, a trial sponsored by the US National Institutes of Health, will be the first trial to study this in humans. This preliminary safety and immunogenicity trial will administer DermaVir to 18 people with drug-suppressed viral loads below 50 copies/mL and CD4 counts above 350 cells/mm3. The investigators will immunize the volunteers with 0.4, 1.6 or 3.2 mg of DermaVir three times at six-week intervals. (Another six volunteers will receive a placebo formulation.)

DermaVir attracted a lot of attention at Glasgow, but the HIV therapeutic vaccine strategy has yet to prove itself after some 14 years of research. It received a new lease on life with the introduction of potent anti-HIV regimens. The drug combinations allow the immune system to function more normally even as their side effects raise qualms about long-term use.

More advanced trials are in progress using anti-HIV drugs plus other therapeutic vaccines, mainly the ALVAC recombinant canary pox vaccine. ALVAC cannot replicate in humans but produces immune-provoking HIV proteins in the cells that it invades after inoculation. Several trials also involve treatment interruptions to see how well vaccinated HIV-positive volunteers can control HIV on their own.

Taking advantage of vaccinated dendritic cells' ability to stimulate the immune system is a new wrinkle, but it is not unique to DermaVir. ACTG trial A5130 uses a method of infecting dendritic cells with ALVAC outside the body and then injecting them back under the source volunteer's skin. This, too, is a preliminary trial. It will enroll 30 persons with drug-suppressed viral loads below 50 copies/mL and CD4 counts above 400 cells/mm3. One arm will receive dendritic cell ALVAC and the other standard injections with ALVAC. Total follow-up time is 66 weeks and will include interruptions in anti-HIV drugs. There will be no information on how effective dendritic cell vaccination is in humans for some time. A comparative evaluation of different vaccines and vaccine strategies, if any of them seem effective, is yet further off.

The Glasgow conference was another demonstration of how much in HIV therapy remains unresolved, if not downright mysterious. On all these topics, further data are expected at the Conference on Retroviruses and Opportunistic Infections, the US national HIV research conference that will take place this February in Boston.

Morocco's Bold Experiment: Treatment as Prevention

by Anne-christine d'Adesky

Sefrou, Morocco is a picturesque mountain village with a minaret-laden mosque and a maze of shops and streets leading to a central square, the medina. Ancient caravans used to wend their way through Sefrou and the surrounding lake and forest country. They were headed for the fabled Tafilalt oasis far to the south. Today, many tourists visit the old city of Fez, which is just an hour away, but the modern world passes Sefrou by. Yet it is in isolated places like Sefrou, amid the cacophony of Berbers selling their wares and muezzins calling the faithful to prayer, that Moroccan health officials will have to measure the success of a bold new AIDS healthcare experiment.

Advocates believe that the new plan coupling access to HIV treatment with expanded testing and services in rural areas will spur those who are now afraid to get tested. That will uncover the truer face of AIDS and help physicians identify patients at earlier stages of infection. Health officials can then target prevention efforts to stem any outbreaks that emerge.

The Embryonic Epidemic

By initiating a national treatment plan now, Morocco is in the enviable position of contemplating whether it can stop AIDS in its tracks. The country has a tiny epidemic — only 1,060 reported AIDS cases by last September 30. But since few people are now tested for HIV itself, no one really knows how big the epidemic is. The first AIDS cases occurred in the mid-90s among urban sex workers, gay or bisexual married men and a small number of intravenous drug users. Heterosexual transmission is becoming increasingly common, putting women at greater risk.

At present, the Ministry of Health estimates that 15,000 to 20,000 Moroccans have contracted HIV. One harbinger of an expanding AIDS epidemic is the dra-

matic rise in other sexually transmitted diseases. Up to 600,000 cases are recorded annually.

"If this situation appears less dramatic than in other regions of the world, it is still very worrisome," stated Dr. Hakima Himmich in Casablanca. Himmich is the dynamic head of the Association de Lutte Contre le SIDA (ALCS — the Association to Fight AIDS). She is also a key figure in the national treatment push. "There is mostly silence about AIDS, and a lot of discrimination, so you understand why people hide it."

Himmich ironically cited the lack of AIDS prevention programs as critical to blocking expansion of treatment. "The obstacles are not at the level of the Ministry of Health. Up to today, there has never been a national prevention campaign. There is no political engagement because the epidemic has just started." But she warned, "If we don't push them, we'll have what was seen in other countries — 10% of the population infected before they wake up. We want to try to avoid that."

Treatment is a way to keep the epidemic down, Himmich believes. "I think stigma can change with access. The minute a mortal disease becomes a chronic one that you can treat, this is where you will see the change happen. It's clear that you can't have an effective prevention strategy without access to care for affected people." But there is a paradox involved. Although she is convinced Morocco can help document the theory that treatment access strengthens prevention efforts, she is not sure how to offer concrete proof if HIV remains rare. "I don't know how to show it works so that it can serve as a model because people could say, 'Well, you didn't have many cases because the epidemic started late and you are a Muslim country.' How do you measure something that doesn't take place?" she muses. "How can you validate such a model? It won't be easy."

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Accommodating Islam

Morocco's move is being closely watched by its Arab neighbors, from Algeria and Tunisia to impoverished Sudan and Somalia. All have relatively low official HIV rates and lag behind in their response to the AIDS epidemic. Given the region's strategic location, sandwiched between Western Europe and hard-hit sub-Saharan Africa, there is concern that the epidemic could take off here, fueled by such factors as poverty, migration and illicit drug use. Morocco remains a developing country with a large rural population of poverty-stricken Berbers and Arabs. Despite pockets of thriving urban commerce, unemployment hovers at 25% and illiteracy is high, around 40% for men and 70% for women. Child labor is an endemic problem, as is the homelessness of rural youths, who migrate to the towns and fall into prostitution or drug trafficking.

The Royal Kingdom is led by 38-year-old King Mohammed VI, a moderate leader who has carefully balanced secular policies and Islamic law. His government is facing pressure by radical Islamic groups, including the Party of Justice and Development, which scored an historic breakthrough in the September elections, gaining 42 of the 325 seats in the parliament's lower house. AIDS activists worry that an ultraconservative religious backlash could hamper the nascent anti-AIDS effort as well as reverse gains in women's status.

Some analysts feel religious taboos on sexual topics have blocked prevention efforts and helped stigmatize HIV-positive individuals. Others claim that Islamic law, with its traditional segregation of men and women and its ban on homosexuality and extramarital sex, has countered the spread of HIV in the Arab world. Morocco's religious leaders have either stayed silent on the subject of AIDS or denounced prevention efforts, arguing, for example, that condoms promote infidelity. One well-known leader publicly declared that belief in Islam was enough to protect the faithful from AIDS.

"Sometimes we fall upon someone who is open, but most of the time they just say the response should be abstinence," said Himmich, who deemed this message "totally counterproductive." But she is the first to agree that, in the future, prevention messages can succeed only if they are integrated into Moroccan culture. "We won't have the same prevention discourse here as in France or Sweden —that's clear. We're going to keep our society in mind, which is Muslim and North African and has its characteristics that we must respect, in order to not shock the public." But, she admitted, thats easier said than done.

Sex Workers and Their Husbands

All of which leads back to Sefrou and the local Berber population, whose customs, language and nomadic movements have kept them on the economic and social margins. Many Berbers lack schooling and are illiterate. In Sefrou, Berber women spend their days sitting outside the former shops of Jewish merchants who fled to Israel when Morocco became independent in 1956. Until recently, they survived by working as prostitutes, turning the old Jewish shops into mini-brothels. Among the Berbers, sex work is not highly stigmatized, but is viewed as something of a family trade passed along from mother to daughter. Regardless of Islam's bans, these women rarely lacked for clients. All that changed this past spring, when radical Islamists succeeded in outlawing prostitution in Sefrou. The Berber women are now destitute. "These women have no future," coolly declared a young Muslim Sefrou resident. "We reject them because they are not pure and no one will marry them. And if they can't make money for their families, they are of no use to anyone."

The question remains, how many are HIV-positive? What about their husbands and male clients? Again, without widespread testing, no one knows for sure. An ALCS study found that 65% of HIV-positive female sex workers were exposed to the virus by their often-older husbands.

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"I hate to say it, but the biggest single risk for Moroccan women with HIV has been their husbands," said Himmich. "That fact makes it even harder for us to confront the problem, because the husbands are in denial and they blame their wives. So you see it's really a social problem that affects the whole family and community." Doctors at the Ibn Roch hospital in Casablanca, one of two specialty centers treating AIDS patients, confirmed that women lag behind in getting tested and accessing care. "We've had a problem with certain Berber patients about telling their wives," said Adnani Kadmiri Said, head of ALCS's treatment education program. "Sometimes they bring the wife, and she is followed too. We know it's a problem, but what can we do? We can't force them to bring their wife, not easily."

Many of the husbands had ultimately fallen sick and died of AIDS. Past surveys revealed that almost half of HIV-positive prostitutes in the country were divorced or widowed and were struggling to raise their children alone. They rarely used condoms with clients, who generally rejected any such proposal.

Another obstacle is widespread ignorance of AIDS. For example, one HIV-positive man admitted to ALCS counselors that he had deliberately sought out young virgins for sex and marriage in order to cure himself of AIDS, a myth prevalent elsewhere in Africa.

There are other signs that HIV may be spreading underground. Random testing in an orphanage in the south recently turned up a surprising number of HIV-positive infants. "That means that there are sex workers who are positive and give birth and abandon their infants," Himmich grimly concluded. HIV testing is not routinely offered to pregnant women in public hospitals or private institutions.

First Steps

To its credit, Morocco is now moving quickly to turn its ambitious treatment plan into practice, and luckily, it holds several aces in its hand. A major one is money, the biggest hurdle. A $9.24 million grant from the new Global Fund to Fight AIDS, Tuberculosis and Malaria will help pay for HIV drugs, diagnostic tests and basic hospital supplies such as gloves and gowns. European donors and other agencies have promised to throw additional money into the pot, as will the government. The funds will provide treatment education and training to both health professionals and patients. In 2000, GlaxoSmithKline provided a two-year grant for patient treatment education; a French foundation will now pick up the tab. Other French groups such as AIDES and ACT UP-Paris have provided medicine and supplies to ALCS over the years and have promised further support.

The main leadership has come from pioneering physicians like Himmich, who is viewed as a force of nature by her admiring colleagues. "She's ten of us in a single woman's body," joked Mustapha Sodqi, a genial physician and ALCS member. "Without her, I don't know where we'd be with the AIDS situation." The ALCS was set up in 1998 as a voluntary agency that provides prevention and other services in 11 cities, with Casablanca as its national headquarters. It cites a laundry list of early victories, some shared with other nongovernmental organizations and the Health Ministry:

early educational and prevention campaigns in Casablanca, Agadir, Marrakech and Fez; forums in schools, prisons, the army and police; launch of an AIDS hotline; support groups and legal assistance to people with AIDS; and the establishment of eight anonymous, voluntary HIV testing sites.

Before 1999, Sodqi explained, ALCS provided 80% of the medicine used to treat poor HIV patients in one or two hospitals in Casablanca and Rabat. These were often donated recycled supplies from rich countries.

In 1999, the Health Ministry kicked in money for two AIDS drugs — AZT and 3TC. Patients paid for the third drug themselves, until a grant from the French Therapeutic Solidarity Fund (FSTI) provided 2.7 million dirhams (approximately US $260,000) for this. ALCS also managed to convince insurers to cover the cost of HIV care for workers. But the cost of medicine remains too high for poor patients, including such opportunistic infection therapies as ganciclovir for cytomegalovirus (CMV), fluconazole for fungal infections and interferon for hepatitis. Most tests are free for HIV patients at Ibn Roch, but not all. Elsewhere, hepatitis B and C testing is not available in public hospitals.

As the global treatment access battle heated up in 2001, ALCS joined with Doctors without Borders (MSF — Médecins sans Frontières) to explore the availability of generic HIV drugs. Two months later, Moroccan officials secured a deal for sharply discounted brand-name drugs through a UNAIDS-backed accelerated access plan designed originally for sub-Saharan Africa. But even at $200 a month, a triple-drug regimen costs more than the average $150 monthly salary of the ALCS clients who are employed — and most are not. As Himmich discovered, the discount deal was in any case less than it seemed. "GlaxoSmithKline and Boehringer Ingelheim dropped their prices, but Bristol refused to even meet with us," she complained.

As of August, 130 people were receiving a three-drug combination, but another 182 were standing by. The new grant from the Global Fund will cover all patients who need medicine through 2004. MSF also has a small project that tests and provides treatment for sex workers. But with expanded testing, the patient population should expand. The end could be new drug shortages.

In late July, a follow-up ALCS-MSF forum took place to determine whether Morocco is ready to pursue generic HIV production. The answer was a qualified yes, from key players like the Health Minister and

local generic drug manufacturers like Gallenica. Major international players were at the conference too, including representatives of Indian, Thai, Brazilian and US generic companies, as well as the World Health Organization and activists from ACT UP and Health Gap. How quickly the government will move depends on many factors, but the main ingredients are there. Or were. The meeting took place before the September advance by the religious bloc. If the political climate changes in Morocco, so could political will.

The True Picture

Nothing underscores the plight of people with AIDS like impending blindness, progressive madness and death. On the same July weekend that officials debated access to generics, three people died of AIDS at the Ibn Roch hospital across town, including a pregnant woman. Although doctors are more adept at treating HIV patients there, many patients are still referred late. "We offer them antivirals but to be honest, triple therapy hasn't done much for these severely advanced cases when they arrive with [cerebral] toxoplasmosis, et cetera," said Dr. Rajaa Bensghir, chief of Ibn Roch's infectious disease day clinic. Physicians fail to diagnose early cases, in part because tuberculosis, malaria and parasitic illnesses produce common symptoms such as fever, diarrhea or weight loss. Hepatitis B and C are also common. Right then, she noted, two other patients were going blind from CMV, and she had no ganciclovir to give them. "It's heartbreaking," Dr. Bensghir admitted.

By comparison, those who are diagnosed early generally do well. At the recent International AIDS summit in Barcelona, several posters showed that prompt treatment benefited Moroccan HIV patients. In one three-year study evaluated by UNAIDS, anti-

HIV therapy quickly lowered viral loads in 219 symptomatic patients, a trend that held for 120 weeks. CD4 cell counts increased on average from 150 to 350 cells/mm^3. Hospitalizations dropped by 84%, along with opportunistic infections. But not all benefited: 26 people died, three abandoned therapy, seven had treatment interruptions and a few failed their regimens. Drug side effects were common, though mostly minor, including gastrointestinal problems, elevated lipid levels and liver toxicity. But there were few cases of lipodystrophy. Adherence was also very high. "Access to [HIV drugs] in a country with limited resources is possible provided that it is innovative and truly actively committed," concluded the study authors.

Today, most HIV patients at Ibn Roch hospital are either from the Casablanca-Rabat region or the southern cities of Marrakech and Agadir. Those living in the north go to an infectious disease hospital in Rabat, though many end up in Casablanca anyway. Children are mostly referred to a pediatric hospital in Casablanca. In contrast to a year ago, patients on therapy are now monitored at Ibn Roch's outpatient day clinic, freeing up hospital beds. There, Dr. Bensghir heads a small team of doctors and nurses, with outside specialists on call. Lab work is performed at the clinic, including CD4 and viral load tests. Patients return monthly for check-ups. If they live far away, they are sent back to their referring physicians for follow-up. This is not ideal, admits Dr. Bensghir, since local doctors aren't trained to monitor patients on HIV therapy.

A lingering hurdle, aside from side effects, has been a big pill burden for patients because certain doses of drugs are lacking. "With Retrovir [AZT], which comes in 500 and 600 mg forms, we have just the 100 mg tablet, so we give them five pills a day," Bensghir explained. "That's just one of the three drugs."

Pediatric drugs are another problem. "We have a pregnant woman who is about to deliver and we have no liquid AZT," said Bensghir. "This is our daily reality." Fortunately, there have been few maternal HIV cases at the center so far. The ALCS has provided HIV transmission prophylaxis, initially AZT plus 3TC, to pregnant women who test positive, but at present only AZT is available.

Pregnant women who need it for their own HIV now receive triple combination therapy. After delivering, the mothers receive free infant formula from ALCS to avoid transmission through breast-feeding. To help these women avoid disclosure of their HIV status to family or community, ALCS counselors suggest a white lie. "They simply say, 'We don't make enough breast milk,' and this explains why they can't breast-feed," mentioned Bensghir, grinning. "That is a common problem for women. But it works."

Stigma and discrimination continue to face those trying to access care elsewhere. The ALCS has confronted dentists and surgeons who won't treat HIV-positive patients or refuse to do C-sections in pregnant women. The agency is forced to provide extra sheets, gowns, gloves and other materials to gynecologists in other hospitals. "We've had some trainings in regional hospitals, but it's not enough," said ALCS educator Said. "There's a lot of stigma, even among doctors. Education and training of health professionals is a real priority."

As they wait for the big money and drugs to be delivered, life remains uncertain for patients now requiring treatment. "In the beginning we had to choose which patients to start on therapy. We were confronted by families: why this patient, why not this one? That was an enormous problem," stated Bensghir. "We'd really like to have treatment for all of them. It's hard to have an illness and be isolated. Some of my patients have been on treatment for three years. But the minute we begin talking they are in tears, even if they are in good health. They are really suffering. We have to manage to help them.

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