

November 2003

**amfAR**<sup>™</sup>  
AIDS RESEARCH

# The amfAR Treatment Insider

## Contents

- 1 HIV Generics
- 2 Learning from Tuberculosis
- 6 Falling for Fuzeon?

## HIV Generics: Ready for a Revolution?

by Anne-christine d'Adesky

In August 2003, South Africa's largest generic drug manufacturer, Aspen Pharmacare, announced a plan to produce a generic combination of three HIV drugs that will sell for under a dollar a day per person. Aspen launched the first generic antiretroviral drug made in Africa, Aspen-Stavudine, earlier in the month. The drug is produced under an exclusive voluntary license from Bristol-Myers Squibb, which markets stavudine (d4T) as Zerit. With similar licenses from GlaxoSmithKline and Boehringer Ingelheim, Aspen submitted applications to the country's Medicines Control Council for approval of its generic versions of zidovudine (AZT), lamivudine (3TC), Combivir (AZT/3TC), didanosine (ddI), and nevirapine.

The news comes on the heels of an historic August 8 decision by President Thabo Mbeki's administration—long opposed to the use of antiretrovirals—to develop a national HIV treatment plan by October in the country with the worst AIDS epidemic in the world. South Africa has nearly 5 million HIV-positive citizens, but only a small fraction currently has access to HIV treatment. At least 600,000 need antiretrovirals immediately. A government Health and Treasury task force

outlined a menu of options for rolling out treatment through the public sector, analyzing drug costs balanced against extended survival. Providing antiretrovirals to 20% of people in need would result in treating 200,000 people by 2008. Full coverage for all AIDS cases would result in 1.2 million people receiving antiretrovirals within five years.

This pivotal event reflects a major victory for AIDS activists from South Africa's Treatment Action Campaign (TAC), who have long advocated for use of generics in their campaign for HIV treatment. In one of the opening salvos of the drug access battle, TAC members illegally imported generic fluconazole from Thailand in 2000 to treat opportunistic infections. TAC recently upped the ante by allying itself with frontline physicians to create the Generic Antiretroviral Procurement Project (GARPP), a private company that will act as a wholesale procurer of quality generics. GARPP's launch is a symbol of pent-up frustration over the continued delays in antiretroviral access—a sentiment shared throughout much of the developing world. A combination of politics, limited funds, and unresolved patent issues has largely kept antiretrovirals out

of the developing world so far. If South Africa is a microcosm of the global struggle for access to HIV drugs, things are about to change dramatically—and generic antiretrovirals are paving the way.

### Generic Antiretrovirals at Last?

Spying a market, Aspen said it hopes the government, UNAIDS, and the Global Fund to Fight AIDS, Tuberculosis and Malaria will be major customers for its new products. Aspen follows the lead of Cipla, the maverick Indian generic manufacturer that sparked a revolution in the debate about HIV treatment access for the developing world. In 2001, Cipla offered to sell its three-drug combination to the nonprofit medical relief group Médecins Sans Frontières for \$350 a year, and to governments for \$600. These prices beat even the highly publicized discount programs on brand-name antiretrovirals offered by the big pharmaceutical companies through the United Nations' Accelerated Access

Initiative. Suddenly HIV treatment in resource-poor settings—all but inconceivable at US prices in excess of \$10,000 a year—became a real possibility and fueled demands for antiretroviral access around the world. The World Health Organization (WHO) has declared that by the end of the year, it will release a plan to scale up antiretroviral treatment to reach 3 million people by 2005.

Widespread publicity over Cipla's move set off a race among several Indian companies to make drugs for what they assumed would be a quickly growing global market. Within months, a number of other private Indian companies like Ranbaxy, Hetero, and Aurobindo were competing for sales in the nascent global and domestic markets (see June/July 2002 issue of the *Treatment Insider*, "India's Generics Play a High-Stakes Game"). Meanwhile countries like Brazil, Cuba, and Thailand have been importing raw materials from Indian companies and manufacturing their own generic

## Learning from Tuberculosis: Applying Pooled Procurement to HIV

by Daniel Raymond

As demand for HIV treatment in the developing world grows, all eyes are on Dr. Jong-Wook Lee, the new Director-General of the World Health Organization (WHO) and former director of WHO's Stop TB department. The WHO strategy for scaling up HIV therapy to reach 3 million people draws upon the lessons of TB control, with a number of TB experts advising Dr. Lee. In July 2003, Lee's team announced plans to create a system to help countries buy and distribute HIV drugs modeled after the Global TB Drug Facility—a move with far-reaching implications for generic antiretrovirals.

Widely hailed as a success, the Global Drug Facility (GDF) has provided free drugs to about 2 million people since its 2001 launch, with a target of 10 million by 2005. Through pooled procurement—several buyers negotiating collectively in order to extract higher discounts—the GDF has made a significant dent in the cost of first-line TB drugs. Using competitive bidding processes, average drug prices for a standard six-month course of treatment have fallen by 30%, to under \$10 per patient.

Would this model work for HIV drugs? An April 2003 evaluation of the GDF conducted by McKinsey & Company made a strong case for extending the pooled procurement strategy to antiretrovirals. The potential for cost savings provides the major incentive, but a GDF-type system would also promote "rational" drug use. Rational drug use means simple, standardized treatment regimens—ideally fixed-dose combinations of two or more drugs in a single pill—that are easy to prescribe, easy to take, and minimize the risk of drug resistance. Resistance can result from suboptimal therapy due to poor quality assurance controls for drugs, interruptions in drug access, and improperly prescribed regimens. Pooled procurement enables the GDF to monitor the quality of TB drugs, assure a steady supply, and promote the adoption of a standard first-line regimen using a fixed-dose combination.

These benefits have garnered enthusiasm for the concept of a global procurement system for antiretrovirals from leading TB experts familiar with the demands of HIV therapy. Dr. Anthony Harries of

antiretrovirals through the public sector. Brazil provides universal access to HIV therapy through a combination of state production of generics and aggressive negotiation tactics with patent holders for steep discounts on brand-name drugs (see October 2003 issue of the *Treatment Insider*, “Brazil’s AIDS Model: A Global Blueprint?”). Officials there recently warned Abbott, Roche, and Merck that Brazil would override their patents on lopinavir, nelfinavir, and efavirenz if it could not obtain lower prices.

For big pharma, the pressure is on. In an historic first, generic antiretroviral producers beat out brand-name companies in open bidding by nine Andean countries and Mexico that established a maximum price for HIV drugs. “The Andean agreement is a breakthrough because it sets a worldwide reference price for antiretrovirals that is based on a generic price,” explained Bill Haddad, CEO of Biogenics, a US generic drug producer that represents Cipla.

Negotiators estimate that savings will allow them to treat another 150,000 people.

Some countries in Africa and Asia have also begun using generic antiretrovirals. With a centralized procurement system, Cameroon treats 7,000 people by importing a generic combination costing under \$300 a year per patient. Thailand treats over 10,000 people at similar prices with generic antiretrovirals produced by the state. Despite these successes, out of the estimated 6 million people in the developing world who require treatment, only about 300,000 were on therapy by the beginning of 2003. Brazil alone accounts for almost half of this number. Two years after Cipla’s groundbreaking move, company officials complain that their cheap, high-quality AIDS drugs are sitting inside warehouses in India, while across Asia, Africa, and other poor regions, 8,000 people a day die due to a lack of affordable medicine. Instead of a revolution, there has been a stalemate.

Malawi’s National TB Control Programme argues, “We need standardized regimens in poor countries and the more standardization between countries the better.” Recent negotiations between a bloc of 10 Latin American countries and drug manufacturers, both brand-name and generic, achieved significant cost savings. On a smaller scale, pooled procurement systems are already taking shape through the Generic Antiretroviral Procurement Project, UNICEF, and the International Dispensary Association.

A global pooled procurement scheme for HIV drugs faces several hurdles. As Médecins Sans Frontières’ Ellen ’t Hoen notes, “It’s not just about markets and prices.” Each country has a regulatory body, like the Food and Drug Administration, governing which drugs can enter the country based on quality and manufacturing practices. But the standards and resources of regulatory agencies can vary widely, so a drug acceptable in one country would be considered substandard in another. Pooled procurement works best with the widest possible range of qualified suppliers—for HIV drugs this may require harmonizing national regulatory requirements and drawing upon WHO’s list of prequalified antiretrovirals, which includes some generics. Intellectual property issues pose further obstacles, especially for promoting standardized fixed-dose combinations like the three-

in-one pills produced by Thailand and Indian company Cipla that contain lamivudine (3TC), stavudine (d4T), and nevirapine.

WHO will not release its pooled procurement plan until December. In the meantime, Dr. Lee’s team will be forced to make some tough decisions. Who will control procurement, and what is WHO’s role? How will intellectual property and regulatory issues be coordinated and resolved? Should the use of some antiretrovirals or combinations be restricted? The GDF only provides first-line TB drugs; for access to the second-line drugs used to treat multi-drug resistant TB, countries need to meet the stringent requirements of another group called the Green Light Committee.

Regardless of the mechanism for antiretroviral procurement, the recent history of TB control efforts offers hope for HIV treatment access. The GDF demonstrates that the availability of drugs can crystallize demand for effective treatment, mobilizing resources and strengthening government commitment. If the GDF can provide treatment for 10 million people by 2005, the goal of antiretroviral access for 3 million starts to look more attainable.

**Please send any comments or questions about *Treatment Insider* articles to [reporters@amfar.org](mailto:reporters@amfar.org).**

## The Patent Wars

Why have so few generic drugs reached people with AIDS in Africa and elsewhere? What prevents governments from acquiring or making generics? Funding still remains an obstacle; even current generic prices vastly exceed what most countries can afford without the assistance of international donors. Yet financial support for HIV treatment has been growing in recent years through sources such as the Global Fund and the Bush administration's \$15 billion global AIDS initiative, half of which has been earmarked for treatment.

But money is only half the story. The legal status of generic antiretroviral production and export has been at the forefront of recent battles over global trade policy. The World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property (TRIPS) reconciles disparate laws governing each WTO member country, bringing patent, trademark, and copyright protections up to US standards. Under TRIPS, pharmaceutical companies will enjoy a minimum 20-year monopoly for patents on their brand-name drugs, allowing them to block the entry of generic competitors. WTO member countries must change their intellectual property laws to conform to TRIPS by 2005.

The consolidation of international patent laws will erase the legal loopholes that enabled the production of generic antiretrovirals without breaking patents. Under Indian law, it is legal to copy a patented drug as long as a different process is used to make it. Indian patent laws do not recognize patents on products—the drugs themselves—but rather patents on manufacturing processes. In Brazil's case, patents do not cover the generics manufactured by the state. Thailand only instituted a patent law covering drugs in 1992, so drugs discovered earlier could be manufactured as generics. In 2005, these countries must bring their intellectual property laws into alignment with TRIPS or face trade sanctions.

A WTO ruling adopted in 2001, known as the Doha declaration, exempts the least-developed countries from adopting TRIPS provisions related to pharmaceuticals until 2016. Doha also states that all countries can and should implement WTO patent rules in a manner that puts public health before the commercial interests of patent holders. In practice, this allows countries to override drug patents under certain circumstances through compulsory licensing. By issuing a compulsory license, governments suspend the monopoly rights of patent hold-

ers by licensing medicine production to multiple suppliers, driving prices down. This opens the door to public and private generic manufacturing and ultimately, lower prices. But compulsory licensing is only permitted with medicines "predominantly" for domestic consumption and not for export markets. This creates a catch-22 situation: if producer countries like India, Brazil, and Thailand cannot export generics, poorer and smaller countries without domestic generic industries will have no sources for drug imports.

TRIPS would require these countries to acquire the capacity to make the drugs domestically—an unrealistic hurdle for many. Drug manufacturing is a complex business that calls for purchasing materials, processing, production, packaging, quality control, release of drugs, storage and related controls. In a recent review of the prospects for establishing local production of drugs in developing countries, Warren Kaplan and colleagues at the Boston University School of Public Health found that

***"It is a recipe to severely restrict efforts of developing countries to access medicines and protect public health."***

African economies could not support generic industries efficient enough to compete with multinationals on price. Other developing countries, like the Philippines, have the manufacturing capacity in place, but their HIV rates are too low to justify producing generic antiretrovirals solely for the domestic market. These countries will only have affordable HIV treatment if allowed to import generics.

## "An Unmitigated Disaster"

Paragraph 6 of the Doha Declaration recognized this contradiction, and called for resolution of the issue by the end of 2002—a deadline long since passed due to hard-line US stances during negotiations. The WTO may resolve these issues at the September Ministerial Conference in Cancún, Mexico. [Note: the amfAR Treatment Insider went to press in August 2003.] The Bush administration recently hinted at a willingness to compromise on draft language in the Motta text, an accord that attempts to clarify the paragraph 6 contradiction. The US dropped its demand to limit the scope of diseases that would permit activation of a paragraph 6 solution, a major sticking point in prior talks. By late August, US trade officials had tentatively laid out four conditions for a revision of the Motta text, according to Asia Russell of Health GAP Coalition, a close WTO watcher. The first is that only public generic suppliers could provide drugs designated for "humanitarian" purposes. That would freeze out pri-

vate companies like Cipla. The second condition requires a clause enabling countries to “opt out” of exercising their right to import generics. According to Russell, the “opt out” provision would allow the US to pressure countries to agree not to issue compulsory licenses for imports. The third US condition is a review mechanism or “audit” of how the paragraph 6 solution would be used. The fourth is the request for an “explicit statement” that distinguishes generically produced medicine through special packaging. This would help prevent reimportation of cheap generics into wealthy countries, where they might be resold and undercut sales of their brand-name equivalents.

The WTO debate has been pitched, with little consensus—and few are willing to predict the outcome. Activists view the proposed draft text for resolving paragraph 6 “an unmitigated disaster” and have called on developing countries to block its adoption. “It is a recipe to severely restrict efforts of developing countries to access medicines and protect the public health,” said Spring Gombe, Global Access Liaison to Health Action International and other non-governmental organizations. “This is a call to action.”

Looking ahead, there are two potential scenarios: if the WTO agrees to a pro-generics revision, countries could issue a compulsory license to obtain generic AIDS drugs imported from producer countries, regardless of their ability to make the drugs themselves or the status of drug patents. Even then, feels Russell, there would be many hoops to jump through as articulated in the Motta text. But if no solution is reached, then countries could still legally use compulsory licensing or parallel importing to get or make some older generic drugs, as long as they have the political will and muscle to confront the US.

The US has consistently and aggressively defended the interests of big pharma, and activists say that many countries have held back from introducing generic antiretrovirals due to fear of US reprisal. Both the US and big pharma have tried to block countries from taking measures legal under TRIPS that would facilitate access to generic HIV drugs. In 1998 South Africa faced a protracted lawsuit by 40 major pharmaceutical companies seeking to block the new Medicines Act that governed pricing and promoted access to drugs. Big pharma eventually dropped the lawsuit in the face of global pressure, with TAC playing a pivotal role in mobilizing outrage. In 2000 the US filed a WTO complaint against Brazil, later

dropped but widely perceived as an attack on Brazil’s high-profile antiretroviral strategy. Also in 2000, GlaxoSmithKline issued legal threats over the importation of Cipla’s generic version of Combivir in Ghana. The United Nations Development Programme’s Human Development Report, issued in 2001, concluded that “pressure from Europe and the United States makes many developing countries fear that they will lose foreign direct investment if they legislate for or use compulsory licenses.” According to Russell, “big pharma and the US government continue to threaten access to cheap medicines, collaborating to oppose entry for India, Brazil, Thailand, China, and other supplying countries to developing country markets after 2005, when TRIPS rules come into full effect.” In the meantime, the unresolved paragraph 6 paradox makes it difficult for countries to plan on long-term access to generic antiretrovirals.

Beyond Cancún, there’s the looming 2005 WTO deadline, when member countries must adhere to TRIPS rules upholding patents. The least-developed countries have until 2016 to do this. In two years, Brazil, India, and Thailand will no longer be able to make generics for new drugs as they can now. Finally, there is the proposed Free Trade Area of the Americas—a successor to the North American Free Trade Agreement. The next round of talks takes place in November in Miami, aimed at establishing a 34-country “free trade block” by 2005. “The US wants to export US-style patent protection, which exceed levels of protection guaranteed under TRIPS,” said Russell. “If the US gets its way, there would be an extension of patent terms past 20 years. There would be a five-year block on any country doing a compulsory license once a patent gets filed. So it has the potential to dramatically limit access to medicines in to the future.” Her take on the FTAA: “It’s one more bit of evidence that the US is giving with one hand and taking with the other—we can see now that the promise the US made at Doha was a lie.”

***“Big pharma and the US government continue to threaten access to cheap medicines...”***

### WHO Wants Generic Antiretrovirals?

Regardless of the outcome of the trade talks, the momentum is squarely behind scaling up antiretroviral therapy as more governments commit to HIV treatment plans. WHO is developing several strategies to support the scale up. High on WHO’s list is a pooled procurement system for antiretrovirals intended to streamline purchasing and distribution, reduce drug costs, and assure quality (see

“Learning from Tuberculosis” in this issue of the *Treatment Insider*). WHO is also offering technical expertise and other “best practice” resources to help countries develop their capacity to buy, deliver, and make drugs. According to WHO advisor Jim Yong Kim, they aim “to ensure that access to drugs is not an obstacle in reaching the target of 3 million in treatment by 2005.”

WHO has also played an important role in legitimating generic antiretrovirals by vouching for their quality after intensive assessment. National regulatory bodies like South Africa’s Medicines Control Council oversee generic products for domestic use, but local standards vary and many countries lack the resources for quality assurance. That’s why WHO has become an independent global arbiter of drug quality and “good manufacturing practices.” Generic antiretrovirals from four companies—India’s Cipla, Hetero, and Ranbaxy and Spain’s Combino Pharm—have gotten the WHO seal of approval, landing on its list of prequalified suppliers. For now, generic antiretroviral manufacturing is growing more rapidly in the private sector than the public. Indian and Latin American companies lead the industry for pills, while China and Korea are well poised to supply raw materials for the drugs. State production of generic antiretrovirals has been slower to take off, but there are signs of movement. Brazil is giving \$100,000 technology transfer grants to 10 countries—five in Africa, five in Latin America—to help develop local generics industries for AIDS drugs. The Thai

state producer, GPO, is giving technical help to Ghana, Zimbabwe, and Zambia to set up pilot manufacturing plants. Zambia hopes eventually to supply antiretrovirals to 13 neighboring countries. Nigeria, with its large manufacturing base and skilled population, is also moving forward.

Looking ahead, most countries will likely rely on a mix of brand-name and quality generic drugs to scale up treatment, based on availability and price. Even the US displays a new pragmatism towards generic antiretrovirals, with administration spokespersons indicating that global AIDS funds for treatment would not be restricted to brand-name HIV drugs. The guidelines of the Global Fund—now chaired by Tommy Thompson, US Secretary of Health and Human Services—do not directly endorse generic antiretrovirals, but encourage procurement of quality drugs at the lowest prices. With more competition, prices will fall, while pooled procurement plans could lower costs more. Some see 50-cent-a-day combination therapies in the near future. “It’s clear that generics have completely changed the equation,” said Joep Lange, outgoing president of the International AIDS Society and a key force behind the WHO’s scale-up plans. “If it weren’t for Cipla and other Indian companies, we wouldn’t be talking today about the possibility of treating millions of people. In the end it doesn’t matter whether the drug is a generic or brand name; what matters is that the drug works and is affordable.”

## Falling for Fuzeon?

by Kristen Kresge

The year of the goat: not quite. According to Roche, 2003 is the “year of Fuzeon.” The first in a new class of AIDS drugs debuted in March and three months later at July’s International AIDS Society conference in Paris, Fuzeon was seemingly everywhere. Each day crowds of conference attendees gathered to hear the intricacies of the new medicine and watch Roche representatives inject Fuzeon into citrus fruits. Few conference sessions failed to mention the drug’s impact on HIV treatment, but so far this attention has not translated into a dramatic surge in Fuzeon sales.

Roche, with assistance from the media, hailed Fuzeon (also known as T-20 or enfuvirtide) as a drug that would revolutionize salvage therapy, and big things were expected. As the first HIV entry inhibitor, Fuzeon provides a new option for people whose virus is resist-

ant to many antiretroviral drugs used to treat HIV. Yet Fuzeon has drawbacks—it requires twice-daily injections, resistance to it can develop in the absence of other potent drugs, and it is the most expensive antiretroviral on the market.

Despite the fanfare in Paris, the only new data released on Fuzeon were 48-week findings from the TORO studies (the two large clinical trials that led to the drug’s approval) and an analysis of what predicted success with Fuzeon at 24 weeks. Not surprisingly, these factors were a higher CD4 count and lower viral load at the start, prior exposure to fewer antiretrovirals, and more active drugs in addition to Fuzeon (abstract #116). The 48-week data demonstrated that the response at 24 weeks, on which approval was based, was generally sustained through one year (abstract #LB2).

These results also confirmed that Fuzeon is least effective in people with resistance to all other drugs, but more useful in those who can combine it with new active drugs to which their virus has not developed resistance. Without any other active drugs in their regimens, only 8% of people in the TORO trials had a viral load less than 400 copies/mL through 48 weeks. With just one other drug, the amount of people with viral loads below 400 copies/mL jumped to 29%.

### “A Weak Launch”

Roche and Trimeris, codevelopers of the drug, had expected early demand for Fuzeon would quickly deplete original supplies, which were limited due to the complexity of the manufacturing process. Roche even set up a centralized prescription system to ensure that people who were prescribed Fuzeon would have an uninterrupted supply of the drug. But three months after the first shipments of Fuzeon, the projected rush to access the new drug has not materialized. Between its approval in March and the end of June, only 2,250 new people began taking Fuzeon as part of their HIV therapy.

Limited use of the drug resulted in sluggish sales; Trimeris reported only \$4.3 million in sales of Fuzeon in the second quarter of this year. These low numbers are even more striking given the extensive publicity surrounding this drug's approval. Yet the promotional efforts of Roche and Trimeris have not resulted in a surge in prescriptions. One investor told the *Wall Street Journal* that the launch of Fuzeon was rather weak.

Roche remains confident that it can sell Fuzeon. “It's not a surprise at all for us. Our feeling is that it's tracking quite nicely,” said Heather Van Ness, a Roche spokesperson. Roche recently expanded its manufacturing capacity in the expectation that demand for Fuzeon will grow. In mid-July, Roche even raised its estimate for annual sales of Fuzeon. Van Ness suggests that as more doctors become comfortable prescribing the drug, sales will steadily increase. “It's the first injectable antiviral in the HIV arena. There certainly is a potential for an expanded uptake. At first, physicians were prescribing it carefully just to get experience with the drug,” said Van Ness.

Traditionally, doctors gain experience with new drugs before approval through involvement in clinical trials or manufacturer-sponsored expanded access programs, which provide drug to those who need it but were excluded from trials. Prior to Fuzeon's

approval, only 250 doctors in the US were supplying Fuzeon to the approximately 1,600 people taking the drug, including 1,000 in the two TORO studies. An additional 600 people had enrolled in the early access program, an unusually low number dictated by limited drug supply.

By the end of June, about 1,000 doctors had prescribed Fuzeon for at least one of their patients, according to Van Ness. Such an increase would seem to contradict Roche's suggestion that physicians' willingness to prescribe Fuzeon posed a barrier to expanded use.

In fact, the 2,250 new people taking Fuzeon represent only half of those that currently want the drug, according to Roche's data. An equal amount, as of June 30, were trapped somewhere in reimbursement limbo, waiting to arrange payment for the exorbitant cost of the drug—the average wholesale price of Fuzeon in New York is \$25,334.

For those who cannot pay full price and lack private insurance, access to Fuzeon requires going through a government payer or Roche's patient assistance program, which can provide free drug to people ineligible for state programs. At the end of June, only 250 people had qualified to receive Fuzeon through the patient assistance program.

Everyone else relies on Medicaid or State AIDS Drug Assistance Programs (ADAPs). Though state Medicaid programs and about half of the ADAPs will reimburse the cost of Fuzeon, the process of securing reimbursement is a bumpy road. Each state has different restrictions on approving reimbursement requests and every prescription requires individual verification due to Fuzeon's expense. This is generally not the case for prescriptions of other HIV drugs, which do not receive such high scrutiny from Medicaid and ADAPs. As a result, doctors have experienced a long wait before their patients get financing through these programs, which may contribute to the slow sales of Fuzeon.

“I'm not surprised that they didn't sell much. No one can get it,” said Dr. Robert Murphy of Northwestern University. While waiting for Fuzeon, Murphy's patients are staying on failing drug regimens—combinations that do not fully suppress HIV due to drug resistance. “The problem is, the financing is really complicated,” he added.

Further confounding the financing for Fuzeon is the cost of other HIV medications. In the TORO tri-

als, participants were taking as many as four other drugs. The combined cost for such a drug combination could be as high as \$40,000. Arranging reimbursement from cash-strapped government agencies for such an expensive combination therapy could cause additional delays.

Holdups in Fuzeon reimbursement have even slowed down enrollment into clinical trials of other experimental drugs. Since Fuzeon is most effective in combination with other active drugs, doctors look for new treatments they can combine with the entry inhibitor. This approach is especially appealing for people with resistance to all other available drugs. Tipranavir, Boehringer Ingelheim's experimental protease inhibitor, is potentially active against drug-resistant HIV, making it an attractive option for use with Fuzeon in salvage therapy. But for Dr. Joel Gallant, director of the Moore HIV Clinic at Johns Hopkins Hospital, delayed access to Fuzeon is preventing some of his patients from entering a phase III trial with tipranavir. "I have been having an incredibly difficult time getting patients the drug," said Gallant.

## Injection Complications

Despite the advantages of combining Fuzeon with new drugs like tipranavir, not everyone is waiting until new treatments are available. Fuzeon can have a lasting benefit even for people who use it without other active drugs. For Matt Sharp, director of Treatment Education at the Test Positive Aware Network (TPAN) in Chicago, taking Fuzeon for a year and a half has meant going back to work after disability. But the decision to try the drug really depends on how aggressive you are with your treatment, according to Sharp.

"I'm able to come back to work, and my energy is boundless," said Sharp, whose CD4 count has been gradually increasing since he began taking Fuzeon in a clinical trial. "But I certainly understand why people wouldn't want to go on a twice-daily injectable drug. It's an individual choice. It just depends on how tolerant you are," he added.

Fuzeon causes painful injection site reactions, which seem to persist throughout therapy. One worry is that over time, suitable sites on the body for injecting Fuzeon will become limited due to the longevity of the reactions. Sharp is still battling these nasty reactions, though the injections have become a part of his daily routine.

Others are more reluctant to use Fuzeon. Both Gallant and Murphy have had patients who avoid taking the drug, choosing to stay on failing drug regimens.

Roche acknowledges that injections are a barrier to Fuzeon's adoption. Van Ness also admits that the complicated process of reimbursement originally caused problems in the distribution of Fuzeon. These delays continue to shape many doctors' perceptions of the obstacles to Fuzeon access, despite efforts by Roche to accelerate reimbursement. Now, according to Van Ness, it should take approximately two weeks from the time a prescription is received to ship the drug. Some delay is inevitable; along with verifying payment, Roche also has to guarantee at least a six-month supply of the drug for all patients.

Roche and Trimeris announced in Paris that more Fuzeon would be available this year. Initially, they predicted that the complex manufacturing process would hinder its availability, providing enough for only 12,000 to 15,000 people worldwide in 2003. In July, Roche announced that Fuzeon would now be available for at least 18,000 people this year—10,000 to 12,000 in the US. "Our supply is greater than we anticipated, but it is still limited," said Van Ness.

Whether demand for Fuzeon will catch up to this increased supply is anyone's guess. Fuzeon is not a simple drug to take, but it may be a long time until an entry inhibitor comes in an easy-to-swallow pill. For now, "it's too early to make any forecasts," said Van Ness, referring to future Fuzeon sales. "I don't think it's something to worry about yet."

**amfAR**  
AIDS RESEARCH

### Treatment Information Services

Gretchen Schmelz  
**Program Director and Editor**

Daniel Raymond  
**Guest Editor**

Elizabeth Paukstis  
**Managing Editor**

Kristen Kresge  
**Staff Reporter**

Melissa Laurie  
**Editorial Assistant**

Bernard Boey  
**Webmaster/Art Director**

W. Keith Henry  
**Medical Consultant**

**Graphics/Design**  
Raoul Norman-Tenazas  
Yolande Hunter

**Spanish Translation**  
Grupo de Trabajo sobre  
Tratamientos de VIH (gTt)  
Barcelona, Spain

**French Translation**  
Haiti Medical, Rochester, NY

**Chinese Translation**  
President Translation  
Service Group International

©2003 All rights reserved.