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Paying for Life
The Issues Behind Drug Pricing

By Bob Huff

Most people today appreciate the value of antiretroviral therapy, if not its price. This is because the price of expensive anti-HIV medications in the U.S. is largely, and thankfully, invisible. Although uninsured or underinsured people with HIV may have to pay for their drugs out of pocket, the cost of pharmaceuticals for most HIV positive Americans is borne by private insurance or by the government through Medicaid or a state AIDS Drug Assistance Program (ADAP). Copayments collected by the pharmacy—which can be a significant burden in themselves—are as close as many people get to the byzantine world of prescription drug pricing.

The happy fact is that thousands of people are alive today because of better medications and generous access that came about during the strong economy of the 1990s. But with Congress feeling less charitable these days, the trouble signs are clear. Increasingly, it seems that if the political will to pay the price of quality health care does not soon find a powerful voice, the combination of shrinking funding and runaway drug costs could put the health of large numbers of people in this country at risk. Already, historic—and possibly catastrophic—changes to Medicare and Medicaid are being decided, all driven by the unbearable cost of medications. Yet none of the proposed solutions attack the underlying problem. The implications for those with HIV are considerable, since drugs are generally the biggest contributer to the price of their continued health.

Rising drug prices affect the cost and quality of health care for nearly everyone in the U.S.

The Increasing Cost of U.S. Health Care

The U.S. is one of the only wealthy nations without universal health care or government limits on the price of prescription drugs, and American health care costs continue to spiral upward, with pharmaceuticals leading the way. Even though most consumers do not bear the cost of their drugs directly, rising prices affect the cost and quality of care for nearly everyone in the U.S. by way of increased insurance premiums, larger copayment amounts, and cuts in publicly-funded programs such as ADAP. As state governments explore ways to control costs, the powerful pharmaceutical industry is fighting to preserve the freedom to set prices without restraint in their largest and most profitable market in the world.

The drug industry has become addicted to revenue growth, which it tries to sustain in every possible way. Continually raising prices has been the central strategy, and U.S. prices have increased at more than double the rate of inflation every year for over ten years. Due to regulation, prices can't grow that fast anywhere else in the world, so the burden disproportionately falls on the U.S., which now

Through the Roof
The issues behind drug pricing 1

One for the Blipper
Viral load and replication rates—where's the link? 8

ATAC Meets FDA
Warm and fuzzy in Rockville 10

Some Things Never Change
Carlton Hogan on demanding post-marketing monitoring of drug safety 12

accounts for over half of the world's pharmaceutical sales. Increasing the volume of drug sales has been the other main engine for the industry's growth over the past decade, and since the advent of direct to consumer advertising in 1997, more U.S. customers than ever have begun demanding drugs for the ailments they see on television. Another profitable strategy has been to switch consumers from older, cheaper drugs to more expensive ones. Marketing is crucial to get doctors to switch patients to "new and improved" versions of drugs that mainly exist to push profits up a notch. Yet there are limits to how far this can be taken. Expenses for sales can be double what a company spends on scientific research, and increased spending for marketing in turn drives the demand for revenue growth. Lately, growth has been obtained by the consolidation of smaller firms into pharma powerhouses, but while these mergers may result in some cost efficiencies, the effect on the bottom line is short lived – and the effect on the creative output of the research departments has been disastrous. Growth arising from true innovation by the pharma giants is becoming increasingly rare.

Since the advent of direct to consumer advertising in 1997, more U.S. customers than ever are demanding drugs for the ailments they see on TV.

Meanwhile, government entitlement programs dig deeper and cut services to pay for drugs, and private insurance premiums have become all but unaffordable for anyone without coverage through a well-paying, full-time job. In today's economy, with unemployment high and many small businesses unable to meet the burden of escalating premiums, one in four Americans lack health insurance, and their ranks are growing.

Sorry, You're not on the List

Over the past couple of years state governments have begun to fight runaway drug costs by attacking the problem on two fronts. First, there has been an attempt to limit utilization by requiring doctors to obtain prior authorization for expensive drugs that are not included on a state-approved formulary list. In practice, the hurdle of seeking approval to prescribe certain drugs means that doctors often select a similar, cheaper substitute. Problems arise when patients are told at the pharmacy that their prescription cannot be filled because it is not on the list; many are likely to give up and go untreated. This sort of manipulation—along with the political red meat issue of cracking down on waste and fraud—may produce some small savings, but in reality, people with complex chronic diseases risk having their care compromised by these restrictive rules. Certainly any effort to cut utilization of anti-HIV medications would be met with anger and outrage.

On the price front, some states such as Michigan and Maine have been trying to win discounts from pharmaceutical manufacturers in exchange for adding their drugs to the approved Medicaid formulary, thus removing the barrier to prescribing. This is a powerful stick to wield, since drug companies are loath to yield any market share to their competitors. The pharmaceutical industry deplores this tactic and has fought back with courtroom challenges, sophisticated public relations campaigns, and drug giveaways via company-run disease management programs aimed at Medicaid patients. In Florida, the pharmaceutical lobby prevailed on Governor Jeb Bush to water down state formulary restrictions by allowing drug companies to offer case management of "high utilizers" instead of discounts. But the industry recently suffered a setback when the Supreme Court decided to allow a program to go forward in Maine that seeks additional rebates for its Medicaid drug purchases. Companies that don't comply will see their products parked on a prior authorization list.

At the federal level, a proposed drug benefit for Medicare beneficiaries has emerged in Congress that many say will provide a windfall for the pharmaceutical industry by dramatically expanding their markets without challenging the current pricing structure.

Why Is Price a Problem?

High prices can become a problem when a drug is available only as a brand-name product from a single manufacturer, as is the case with antiretrovirals in the U.S. Every approved anti-HIV drug sold in this country is still under patent protection. A patent guarantees the holder an exclusive right to market the protected product without competition for a period of at least 20 years. After the patent protection period has expired, other manufacturers are free to produce a nonbranded, generic version and sell it at a fraction of the price of the branded drug. In the pharmaceutical business, a good example is the case of fluoxetine (Prozac), which sold for $2.50 per pill until its patent ended in 2001 and a generic manufacturer brought its version to market for only $0.25 apiece.

The first anti-HIV drug expected to lose U.S. patent protection is AZT (zidovudine, Retrovir), which could become available generically in the U.S. sometime after 2005. Since most people who use AZT these days take it with 3TC (lamivudine, Epivir) in the form of Combivir, generic AZT is unlikely to have much impact in this country.

Several generic antiretrovirals are now produced in countries such as India and Brazil and these are promising to help to make treatment a possibility for millions of people who could never hope to afford expensive branded medications. One of the ironies of the marketplace is that some generic makers are now producing practical and convenient all-in-one formulations of individual drugs controlled by different patent holders. One such product, Triomune, is a combination of nevirapine, d4T and 3TC. Such drugs may be available for pennies a day in the developing world, but are unavailable in the U.S. A recent announcement by the Clinton Foundation indicates that manufacturing deals have been struck to bring the monthly cost of treatment to under $20 per person per month—40 to 80 times less than in the States. Although generics have not directly affected the cost of anti-HIV drugs in the U.S., the dramatic gap in prices, separated only by FedEx and U.S. Customs, is making the industry exceedingly nervous.

Historically, when a generic equivalent enters the market, the profit potential of the original branded drug virtually vanishes. The price of the generic is set at some margin above the cost of materials, manufacturing, and distribution, and the maker of the branded drug must lower its price or give up the market. The prices of generic equivalents can be set so low because their makers typically invest little or nothing in drug discovery, clinical research, and marketing.

Major pharmaceutical manufacturers argue that the significant cost of bringing new drugs to market justifies the high prices they charge. Furthermore, since the window of premium pricing is limited by a product's patent life—a good portion of which is used up during the approval process—all of a drug's research and development costs must be recouped within a relatively short period of time. Finally, since drug development is far from a sure thing, successful drugs are called upon to pay for any number of past and future failures.

Critics of exorbitant drug prices point out that the pharmaceutical business, despite its complaints, remains one of the world's most profitable industries, and that development costs are overstated and often subsidized by government. Corporate reports clearly show that R&D expenses typically run at a fraction of what is spent on marketing and reserved for profit. Drug pricing, critics say, is driven by greed and by the monopoly protection allowed by patents. The true cost of high drug prices, they say, is measured in lives lost.

But the generic price advantage may not be a reliable long-term solution to the current drug cost crunch. Consolidations among generic manufacturers are reducing competition, and generic manufacturers—seeing the gap between their prices and those of branded products as a wasted opportunity—recently have begun raising the sticker price on their knockoffs, thus further intensifying the squeeze on state and federal drug budgets.

Risky Business: The Case of T-20

Although the pharmaceutical industry has remained profitable despite the tough economic climate of the past few years, the costs and risks associated with identifying and shepherding a new anti-HIV drug to market are considerable.

The first of a new class of HIV drugs called entry inhibitors brought the issue of pricing to center stage earlier this year. T-20 (enfuvirtide, Fuzeon), discovered by Trimeris and developed and marketed in partnership with Hoffmann-La Roche, entered the market in March 2003 as the most expensive anti-HIV drug ever. With an announced wholesale acquisition cost (WAC) of $20,000 per year, the price at the pharmacy for cash customers reaches $26,400 annually, or $2,200 per month.

The development of T-20 began over ten years ago, and it took five years and $50 million simply to prove it was a viable therapy in humans. Eventually, after ten years and $600 million invested, the drug made it to market, but it is not yet clear how accepting consumers will be of an AIDS medicine that must be injected twice daily. Presumably the population for whom T-20 is intended—those who have developed resistance to most other available antiretrovirals and have run out of therapeutic options—will be willing to put up with the discomfort and inconvenience for a chance at survival. But will that willingness extend to government programs that pay for life-saving medication for people with HIV, especially in perilous economic times? Maybe not. Already some ADAPs have refused to put Fuzeon on their formularies, and now Roche has told activists that its patient assistance program (PAP) won't cover elegible patients in states where ADAP doesn't pitch in.

The risk for Trimeris and Roche is that after all the money and time invested, only a limited number of people will be able to benefit from T-20. The risk for those with multidrug-resistant virus is that a good drug will remain out of reach because the price is simply too high.

Sales of Fuzeon have reportedly been well below expectations and the price of Trimeris stock has dropped by over half since the launch. One way out for Roche might be to snap up tiny Trimeris while it is down. This would cut costs by eliminating royalty payments and put the fusion inhibitor technology into Roche's hands for further development. But maybe that was the plan all along.

Have I Got a Deal for You!

One of the hardest things to understand about U.S. pharmaceutical pricing is that not everyone pays the same price. And the prices for different payers are often secret. The situation is much like passengers on a jet plane all headed to the same destination: no one knows how much the person in the next seat paid for their ticket. The only official price released by a pharmaceutical company is called the wholesale acquisition cost (WAC), which is the list price that industry middlemen are supposed to pay to the pharmaceutical maker. The wholesaler, in turn, distributes the drug to pharmacies for retail sale.

Chain drugstores in the poorest neighborhoods of New York were charging prices well above the citywide average.

A more widely quoted price for drugs is the average wholesale price (AWP), which is an average of list prices quoted by wholesalers to pharmacies. But because of an arcane system of discounts, rebates, and charge-backs, almost no one pays the "official" price. The acquisition cost (AC) is the actual amount that a pharmacy pays for its drug inventory. This cost varies depending on the quantity purchased, as well as on the rebates and discounts available to the pharmacist. Large buyers can obtain significant discounts: you can almost be sure that a drugstore chain like Duane Reade is paying less for pharmaceuticals than an independent neighborhood drugstore, although this may not translate into lower prices for consumers. A recent survey of 155 New York City pharmacies found the highest prices at the biggest chain stores, which charged, on average, eight percent more than mom-and-pop stores. Shockingly, the report also found that chain stores in the poorest neighborhoods charged prices well above the citywide average, meaning that those who can least afford high drug prices in New York are paying the most.

After acquiring a drug, the pharmacy then resells it to consumers with or without an additional markup, plus something called a dispensing fee added on. The dispensing fee is a charge for the professional services of the pharmacist, plus an additional percentage of the drug's cost to cover overhead and profit. Each of these steps may be regulated or fixed by prior agreement. For example, some Medicaid programs may limit the dispensing fees charged by retail pharmacists.

A complex system of rebates for government purchasers has been negotiated to help control drug costs for the large entitlement programs. The size of the rebates paid by the manufacturer varies depending on who pays the bill when a prescription is filled. The average manufacturer price (AMP) is a government-calculated average of prices for a drug actually paid by nongovernment purchasers. Although not officially disclosed, the AMP is estimated to run about 20 percent below the AWP. Government programs use the AMP as a baseline to calculate rebates, with the Medicaid rebate statutorily set at 15.1 percent of the AMP.

For programs that distribute drugs directly to their clients, the Public Health Service has established a discount plan that guarantees something called the 340B price, which at minimum matches the Medicaid 15.1 percent price break, although participating programs are free to negotiate better discounts. Such federally approved 340B participants include hemophilia treatment centers, family planning clinics, and ADAPs that run their own distribution systems. Most big ADAPs, however, distribute their drugs through pharmacies and are organized as reimbursement programs. This means that, for each covered drug dispensed, the state reimburses the pharmacy the AWP minus any special negotiated discounts, plus the dispensing fee. The state then collects its negotiated rebate directly from the manufacturer.

The Best Is not Good Enough

The "best price" is a proprietary federal determination of the lowest price paid by a manufacturer's best customers after rebates and discounts have been applied. Best price is one of the factors used to calculate the rebates owed to state Medicaid programs. Yet certain customers getting some of the best deals are left out of the best price equation.

For example, some government agencies that purchase drugs directly from manufacturers may enjoy extra discounts, which, if included, would bring the average best price down. Another large government purchaser, the Department of Veterans Affairs (VA), negotiates a price that is published as the Federal Supply Schedule (FSS) price. The FSS price is based on what drug makers charge their "most favored" nonfederal customers—which, again, may not be the lowest price in the marketplace if, for example, Wal-Mart negotiates a special promotional deal on atorvastatin (Lipitor). Both the 340B and the FSS prices are also excluded from the best price calculation.

So what is the price of any particular drug? It depends on who's paying and who's asking, since neither the government nor the manufacturers disclose that information. As an example, take tenofovir (Viread), produced by Gilead Sciences. The published WAC is $360 for a 30-day supply; an online pharmacy advertises it for $435; and a state ADAP program may pay

Drug Pricing Terms

340B (PHS) Price: The maximum price that manufacturers can charge covered entities participating in the Public Health Service's 340B drug discount program.

Acquisition Cost (AC): The net cost of a drug paid by a pharmacy. It varies with the size of container purchased (e.g., ten bottles of 100 tablets typically costs more than one bottle of 1,000 tablets) and the source of purchase (manufacturer or wholesaler).

AIDS Drug Assistance Program (ADAP): A federal program established in 1987 to provide anti-HIV and related medications to low-income Americans.

Average Manufacturer Price (AMP): The average price paid to a manufacturer by wholesalers for drugs distributed to retail pharmacies. The Congressional Budget Office estimates AMP to be about 20% below AWP for more than 200 drugs frequently purchased by Medicaid beneficiaries.

Average Sales Price (ASP): A new system created by federal and state governments to ensure more accurate price reporting. ASP is the weighted average of all non-federal sales to wholesalers and is the net of chargebacks, discounts, rebates, and other benefits tied to the purchase of the drug product, whether it is paid to the wholesaler or the retailer.

Average Wholesale Price (AWP): A national average of list prices charged by wholesalers to pharmacies. AWP is sometimes referred to as a "sticker price" because it is not the actual price that larger purchasers normally pay, which is often considerably lower. AWP information is publicly available.

Best Price: The lowest price paid to a manufacturer for a brand name drug, taking into account rebates, chargebacks, discounts or other pricing adjustments, excluding nominal prices. Best price data are not publicly available.

Big 4: The four largest purchasers of pharmaceuticals within the federal government: the Department of Veterans Affairs, the Department of Defense, the Public Health Service, and the Coast Guard. The Big 4 often get pricing below FSS on brand name drugs.

Covered Entities: Facilities and programs eligible to purchase discounted drugs through the Public Health Service's 340B drug discount program. Covered entities include state AIDS Drug Assistance Programs (ADAPs) and hospitals owned by state and local governments.

Dispensing Fee: The charge for the professional services provided by the pharmacist when dispensing a prescription, which may include overhead expenses and profit.

Federal Ceiling Price (FCP): The maximum price manufacturers can charge for FSS-listed brand name drugs to the Big 4, even if the FSS price is higher. FCP information is not publicly available.

Federal Supply Schedule (FSS): The collection of multiple award contracts used by federal agencies, U.S. territories, Indian tribes, and others to purchase supplies and services from outside vendors. FSS prices for the pharmaceutical schedule are based on the prices that manufacturers charge their "most-favored" non-federal customers, which may not be the lowest prices on the market. FSS prices are publicly available.

Federal Upper Limit Price (FUL): The federally established maximum price for a drug if at least three equivalent generic versions of the product are available and at least three current suppliers. FUL equals 150% of the published price for the least costly therapeutic.

Medicaid: A program using state and federal funds to reimburse providers that offer medical care to low-income people who cannot afford health insurance. Medicaid serves 55 percent of people with AIDS and 90 percent of children with HIV/AIDS nationally.

Medicare: A federally administered system of health insurance available to people aged 65 and over and to people with severe disabilities.

Non-Federal Average Manufacturer Price (Non-FAMP): The average price paid to a manufacturer by wholesalers for drugs distributed to non-federal purchasers. The Big 4 are entitled to discounts on brand name drugs of at least 24 percent off of Non-FAMP. Non-FAMP is not publicly available.

Pharmacy Discount Price: The price paid to the pharmacy by a program (i.e., ADAP, Medicaid) for drugs. Brand name drug prices are typically paid relative to AWP (for example, AWP minus 10%). The price covers the pharmacy's payment to the wholesaler, operating costs, and profit.

Unit Rebate Amount (URA): The rebate amount paid by a manufacturer to ADAP/Medicaid for each unit (e.g., capsule) of drug. Information on URA is not publicly available.

VA National Contract Price: The price the Department of Veterans Affairs has obtained though competitive bids from manufacturers for select drugs in exchange for their inclusion on the VA formulary. Because the VA is entitled to FCP prices under federal law, VA national contract prices are even lower than FCP prices and are often the lowest prices in the nation. These prices are publicly available.

Wholesale Acquisition Cost (WAC): The price paid by a wholesaler for drugs purchased from the wholesaler's supplier, typically the manufacturer of the drug. WAC is the price manufacturers release publicly, and is sometimes called the "list price." Publicly disclosed or listed WAC amounts may not reflect all available discounts.

$380. As a point of comparison, Gilead has offered tenofovir to antiretroviral treatment programs in developing countries at $39 per month, roughly the company's cost of manufacturing.

Other Factors Affecting Price

Another aspect of a drug's price is less often discussed: what is it worth to the individual? The advent of the eBay online auction model has rationalized the pricing of all kinds of products and services by offering them to a wide market and letting individual buyers decide what they are willing to pay. But for products that are necessary to preserve human health and life, society has decided that some unregulated markets are unacceptable. Governments and large private health systems such as Kaiser Permanente use their clout as huge purchasers of pharmaceuticals to demand lower prices, and now the states are attempting to control prices with rules, legislation, and group bargaining power. Yet there are ways around these pressures. Statutory discounts can be thwarted by raising the base price until the discounted price matches what the company would prefer the customer to pay. Where price increases for existing products are capped, a company may introduce a new formulation of an old drug at a higher price.

Could we finally be entering an era in which political reality demands more reasonable cost controls?

Some prices are set where they are because that is how much other, similar products cost. For example, there are probably few similarities between the operating costs of cable and satellite television, yet remarkably both services are priced the same. And why does high-speed Internet access via DSL cost the same as access via cable? Well, providers reason, if that is what people are willing to pay, then why leave money on the table? When protease inhibitors (PIs) first entered the market in December 1995, they established a new benchmark for the price of HIV/AIDS medication, and the industry hasn't looked back since. This seems to be a lesson the generic drug industry is now putting into practice.

Some fear a new niche market may be on the horizon as several so-called salvage drugs, which work against highly drug-resistant HIV, proceed through the drug development pipeline. Some potential candidates might be the protease inhibitors tipranavir or TMC 114. Fuzeon (T-20), while best known as the first entry inhibitor, is also primarily a salvage drug. There have been reports of a market research company testing the waters for creating a new pricing category for salvage drugs, with Fuzeon's $20,000 per year price a benchmark. While pricing a difficult-to-tolerate PI that high may seem preposterous on the face of it, the limits of drug company audacity may be revealed when and if these drugs make it to market.

Price also reflects the value offered by a drug. For hepatitis C virus (HCV), for example, the price of a yearlong course of treatment includes the chance that one's infection may be permanently cured. Currently, the newest and best HCV therapies can run upwards of $35,000 per year. But with HIV, there is no cure, and the need for therapy lasts a lifetime. The cost of anti-HIV therapy in the U.S. currently runs between $10,000 and $18,000 per year.

The price of drugs may also be weighed against the cost of hospitalization and care for untreated HIV, and thereby judged to be a bargain. A new, pricier drug may have fewer side effects and require less medical management than its cheaper predecessors. In the big picture, it is a money saver (though in the short term it is still a drain on state budgets). Some economists have calculated the value of drug therapy in relation to lost productivity due to early death from AIDS. Few people who lived through the bad old days before PIs would say that the latest antiretrovirals aren't worth the cost.

Death and Taxes

Could we finally be entering an era in which political reality demands more reasonable cost controls? There are powerful forces influencing elected officials today. Health care costs continue to rise, even as demand is forecasted to balloon as the population ages. Yet the political will to pay for equitable health care remains weak; too few voters accept the connection between taxes and the social benefits that government provides. On the other hand, the biggest contributor to rising costs—the pharmaceutical industry—is represented by an extensive and pervasive lobby that makes significant contributions to influential members of Congress and the Administration. Beyond these commercial and political interests are conservative hardliners who argue that government has no right to levy taxes to pay for other people's problems. These forces would just as soon see Medicaid and Medicare crash and burn; many view the Bush tax cuts as a shortcut to dismantling all entitlement programs. In the ongoing struggle between those who wish to downsize government spending, the taxpayers, and the growing number of people in need of affordable health care, it increasingly looks as if something has to give.

Medicare: the Final Frontier

The major battlefield is turning out to be the question of whether Medicare, the medical insurance program for seniors and people with severe disabilities, will be able to offer a prescription drug plan that doesn't make things worse than they already are. Currently this government program does not cover outpatient prescription medicines. Without substantial extra insurance, people who rely on Medicare pay for their medications out of pocket—which means that those who can least afford it often pay higher prices than almost anyone else.

The plight of seniors has received high-profile coverage on the nightly news, with footage of old folk boarding buses bound for discount pharmacies in Canada. Internet sites that fill prescriptions at the more affordable Canadian prices have come under attack as some major pharmaceutical companies have refused to sell their products to Canadian pharmacies that ship drugs back to the U.S. It is not clear whether there is a significant benefit to shopping in Canada for individuals with HIV: the listed Canadian pharmacy price for a month's supply of 3TC (lamivudine, Epivir) is $230, compared with Walgreens' U.S. price of $295. But recently, some big purchasers have expressed their intention to get into the reimportation act. The governor of Illinois and the mayor of New York have each begun demanding the right to acquire more affordable drugs from Canada and Europe and the principle has gained a surprising amount of support in the House of Representatives.

Faced with change, the industry initially tried to block a Medicare drug benefit, because they feared the leverage the government would gain if it were able to negotiate prices for seniors, the largest sector of drug consumers. As this paragraph from Pfizer's 2002 annual report cautions investors:

"In the U.S., many pharmaceutical products are subject to increasing pricing pressures, which could be significantly impacted by the outcome of the current national debate over Medicare reform. If the Medicare program provided outpatient pharmaceutical coverage for its beneficiaries, the federal government, through its enormous purchasing power under the program, could demand discounts from pharmaceutical companies that may implicitly create price controls on prescription drugs."

Yet the next line in Pfizer's report recognizes that change may present opportunity: "On the other hand, a Medicare drug reimbursement provision may increase the volume of pharmaceutical drug purchases, offsetting at least in part these potential price discounts." The plan that has emerged is beyond Pfizer's wildest dreams.

Congress is now proposing a Medicare revision that, while it may offer coverage to some of those hardest hit with the burden of drug costs, does so with the condition that Medicare won't use its new buying power to negotiate better prices. The impending deal throws a lifeline to an industry addicted to growth by dramatically expanding the size of the U.S. pharmaceutical market without touching the profit potential, in effect giving the drug companies a huge windfall paid for by taxpayers, the grandchildren of taxpayers and by seniors forced to go along with a stingy plan full of hidden, painful cost-sharing provisions.

For thousands of people with HIV, the details of this plan are especially frightening. It's currently estimated that around 50,000 people with HIV are beneficiaries of both Medicare and Medicaid. For these people, Medicaid provides a safety net to deliver essential drugs that Medicare does not. Under the new proposal, people on Medicare would be forbidden to draw on Medicaid benefits for uncovered drug costs, in effect forcing low income Medicare beneficiaries into the already reeling ADAP system or onto the streets. The full implications of these proposed changes still have not been realized.

As the reimportation cause moves to the mainstream and as drug costs become a bigger part of everyone's budget, price controls may no longer seem like a radical idea. House Speaker Dennis Hastert recently awoke to the realization that unfettered drug prices in the U.S. are in effect subsidizing price controls in Europe. Is this the birth of a new red meat issue based on outrage that France is getting a free ride at U.S. taxpayer expense? But Hastert, a foe of reimportation, is more concerned about raising prices elsewhere than capping prices here at home, and he has asked U.S. Trade Representative Robert Zoellick to look into the issue.

Virtually everyone agrees that mounting drug costs are causing distress, but no one has been able to forge a political accommodation that would assure access to needed medications for all, while continuing to support research into newer and better drugs for those who will need them tomorrow. Meanwhile, budgets continue to strain as more and more people come to depend on life-giving pharmaceuticals whose prices rise with no end in sight.

A version of this article originally appeared in BETA.

One for the Blipper

By Bob Huff

You can be a "blipper" and still be chipper, suggests a study in the Noember 2003 issue of the Journal of Virology by Michele Di Mascio and her colleagues from the Los Alamos National Laboratory and the Aaron Diamond AIDS Research Center in New York. Blips are usually thought of as occasional, transient, episodes of low-level HIV RNA viremia in someone who is adherent to their antiretroviral therapy and otherwise enjoys a well-suppressed viral load. Most people with HIV RNA below 50 copies/mL (undetectable) may have intermittent positive viral load test results at some time or another. But how common are blips, how long do they last, and what causes them?

The study's most striking finding is that blips may actually be viremic episodes that last as long as a month.

Some have suggested that blips are due to the release of virions from reservoirs or protected sanctuaries in the body where replication of drug-sensitive virus continues at a low level. Others have reported that it's drug-resistant virus that makes for blips. Another theory is that an immunological event such as an infection suddenly increases the number of infectable immune cells and that blips are the resultant viral feeding frenzy. Whether due to any of these reasons or perhaps due to natural variations in drug levels in a person hovering on the margins of suppression, most studies, fortunately, have not found a long-term association between blips and loss of virologic control or disease progression.

Di Mascio's study looked carefully at the frequency and duration of blips above 50 copies/mL as recorded in 123 treatment naive patients from eight different research cohorts starting a PI-containing regimen. The mean CD4 count at treatment initiation was 474 (+/- 254) cells/mm^3. Overall, the analysis looked at an average of 26 viral load tests per subject over as many months, finding a wide variation in blip frequencies, with 41 patients showing no blips and one patient blipping at every other determination. The average number of blips per sample was 0.09.

The study found that blips were not due simply to assay variation or to chance alone but that different people inherently have different tendencies to blip. They next showed that, within the limits of monthly testing, having one blip does not predict having another and that blip arrival is substantially random. Furthermore, in the patients studied, neither the frequency nor amplitude of blips seemed to increase with time on therapy, which suggests that poor adherence was not responsible for these viremic episodes. There was a relationship, however, between blip frequency and baseline CD4 count, with those having more advanced HIV disease at the time of starting therapy being more likely to become blippers. The significance of this is not clear, although during the period of observation reported here no increase in blip frequency was seen.

Blips Passing in the Night

Perhaps the study's most striking finding is that blips may actually be viremic episodes that last as long as a month, and that, depending on sampling frequency, a number of different blips could produce a pattern of viral load test results that appears as continuous viral breakthrough. An analysis of viral load measurements taken within 22 days of a blip, when fitted into a model, predicts a typical blip duration of 20 to 30 days. If blip episodes actually last this long, then even people with several consecutive detectable viral load determinations might actually be having a train of independent blips, and not sustained viral load throughout the period. Since even sequential blippers in this study generally did not progress to virologic failure, one might wonder how many consecutive blippers in real life have undergone unnecessary regimen switches because of what appeared to be sustained low-level viremia to a clinician determined to maintain undetectability? While this work comes from the Theoretical Division of the Los Alamos lab, the practical implications of blips, blippers and blipping obviously require more and urgent research.

Replication Rates and Viral Load

The different rates and amplitudes of blipping suggest that there is a great deal of individual variability in the replication rate of HIV, even when mostly suppressed by drug pressure. Another study reported in the November Journal of Virology investigated the relation between viral load and replication rate in individuals who are not taking antiretroviral drugs.

It's long been recognized that viral genetics plays a role in how aggressively HIV behaves in a host. The X4 coreceptor-using variant is particularly famous for kicking HIV immune damage into high gear. More recently it's been recognized that for people who have been on therapy and have developed drug-resistance, their

mutant virus may be "less fit" than a wild type drug-susceptible virus. If so, then staying on a failing regimen may be clinically protective despite loss of viral control. Growth competition experiments have also shown that viruses from several long-term non-progressors were inherently less replication competent than viruses from people with normal rates of disease progression.

On the host side, the best known genetic trait that affects susceptibility to HIV infection and subsequent disease progression is a mutation found in a small segment of the population that limits or eliminates the CCR5 cell surface protein, an essential co-receptor for HIV entry. But this flaw in the CCR5 gene is not the only source of CCR5-dependent variability in HIV replication. Even in persons with two functional copies of the CCR5 gene there may considerable interpatient variability in levels of CCR5 expression at the cell surface. Individuals may also express different amounts of RANTES, a messenger protein that competes with HIV for using CCR5, with elevated levels of RANTES associated with slower disease progression. Different degrees of innate and acquired immunity to HIV may also play a large role in keeping HIV replication under control during the years of slowly progressing disease that follows primary infection. HIV-specific CD8 cells in particular are thought to help in controlling runaway HIV disease and it is hoped that one day a vaccine can be made to boost these protective cells.

The amount of virus found in the blood (viral load) is likely determined by a balance between the elimination of virus and the production of new virus. HIV-specific CD8 cells are generally considered the leading candidate for effecting viral elimination. But this theory remains shaky because most studies haven't found the expected correlation between the strength and specificity of CD8 T-cell response and lowered viral load. If CD8s are mainly responsible for clearing out unwanted HIV, then why don't people with the most qualified CD8s always have the lowest viral loads?

Thomas Campbell and colleagues from the University of Colorado, Denver, sought to establish if replication rate was correlated with plasma viral load levels by performing two different kinds of replication rate assays on the viruses of 12 individuals with chronic HIV infection who were not receiving treatment. Eight of the 12 were treatment naive and none of the participants had detectable drug resistance mutations.

Each individual's virus was cultivated in cell cultures for up to ten days with assessments of HIV p24 protein production performed daily. Changes in the amount of p24 detected from one assessment to the next produced a growth curve that revealed each virus' particular replication dynamics. Typically, each virus had a daylong lag before any p24 production was seen. After p24 was detected, growth proceeded exponentially for the next six days or so. Finally, a plateau phase appeared after the sixth day when additional p24 production tapered off, probably due to saturation of infectable cells after day four.

Different viral replication rates may obscure measurement of immune-based factors that influence viral load.

In addition to the growth curves, the replication capacity of each virus' reverse transcriptase and protease enzymes were determined by genetic recombination techniques using a modified version of the Phenosense drug susceptibility assay.

The investigators found a strong linear relationship between replication rate and viral load that held true from 1000 copies to 100,000 copies/mL. Furthermore, they established that, among these 12 individuals, there was significant natural variation in rates of viral replication due entirely to viral qualities. Another interesting finding was that RT and PR replication capacity were related to the cell-based replication rate. This suggests that genetic variations in these wild type enzymes may be responsible for the different replication rates of different viruses, even in the absence of drug exposure.

One limitation to the study is that in cell systems the role of the host's genetics and immune system are removed, so an individual's actual response to their virus can not be predicted from these results. This issue aside, however, the authors make a provocative suggestion that different viral replication rates may be obscuring measurements of immune-based factors that influence HIV viral load in the body. In particular, they suggest that CD8 cell responses, which have previously not correlated well with viral load, should be reexamined after controlling for replication rate. It's possible that the expected CD8 impact on viral load may only become clear after the "noise" of variation in replication rate has been reduced. If so, then this could help unlock one of the central mysteries of immune control of HIV and remove one of the stubborn stumbling blocks in the way of finding a vaccine.

Di Mascio M, Markowitz M, Louie M, et al. Viral blip dynamics during highly active antiretroviral therapy. JVirol. Nov 2003.

Campbell TB, et al. Relationship between in vitro human immunodeficiency virus type 1 replication rate and virus load in plasma. JVirol,.Nov 2003.

Treatment Activists Meet with the FDA

By Bob Huff

HIV treatment activists met with officials and staff of the federal Food and Drug Administration (FDA) on November 14, 2003 in Rockville, Maryland. The FDA hosted the meeting to update the community on several recent drug approvals and to address several questions that activists had been asking about the future of drug approval for HIV in the U.S. The event was a field trip for staff of the Center for Drug Evaluation and Research (CDER), with at least 30 scientific and clinical staff in attendance. The activist community was represented by 25 members of the AIDS Treatment Activist Coalition (ATAC).

The community is asking for better systems to monitor long-term side effects after drugs have been approved.

Mark Harrington opened the forum by recapping the history of HIV drug development from the community perspective. Some FDA staffers may have been surprised to learn that fifteen years ago, on October 11, 1988, over a thousand AIDS activists had surrounded their headquarters and shut down the agency for a day in protest of slow drug approvals and unethical study demands. Harrington recounted how relations improved dramatically after that, and that cooperation between the community and the FDA during the term of Commissioner David Kessler in the 1990s helped speed the approval of an unprecedented number of new drugs that altered the course of the U.S. epidemic. He also noted the leadership role the agency has played by holding hearings about emerging challenges in HIV drug development before they become widely recognized, and for makeing the industry informed about what is expected of them early in the approval process.

Harrington then summarized the community's requests:

- More data on pharmacokinetics of drugs in more diverse populations
- More drug-drug interaction studies completed at the time of approval, including studies with methadone, birth control hormones, and TB drugs such as rifampin.
- Drug-drug interaction studies with the most commonly used protease inhibitors and NNRTIs should also be performed.
- Industry should be consistently prodded to assure that study populations reflect the makeup of the epidemic by adequately representing women and people of color. The composition of study populations is usually set at the time the study sites are selected and it will be important to build new relationships with clinics capable of enrolling more diverse groups of individuals.
- After drugs have been approved, promises made by companies to continue post-marketing research should not be allowed to languish. Currently the agency has no effective way to compel completion of these Phase IV commitments, and pressure on Congress to give the FDA more leverage may be needed.
- The community is also asking that better systems be implemented to monitor long-term side effects after drugs are approved. The current adverse events reporting system is voluntary and may miss early signals of toxicity. A network of "sentinel practices" that would report unusual symptoms might be a viable enhancement to our early detection system. The need for a better system to detect and track side effects such as lipodystrophy syndrome after drugs are approved is a top concern for ATAC.

In addition to these drug development issues, ATAC members expressed concern about reports that ideologically biased individuals had been inappropriately appointed to sit on FDA advisory committee panels that review drugs concerned with reproductive health. There was also concern that radical deregulationists who view the FDA as a roadblock to free and unfettered business would seek to dismantle the Agency.

Current commissioner Mark McClellan joined the meeting, thanked the community for its important contributions and responded to the issues raised by ATAC. In particular he outlined a prototype adverse events surveillance system being developed in association with the National Cancer Institute. McClellan has made better safety reporting a priority for the agency and the pilot model for cancer should be implemented for HIV as soon as possible.

The commissioner also addressed activist concerns about politicization of the agency, radical deregulation and reimportation of prescription drugs from Canada and Europe. He denied that politicization was occurring or that the agency was in jeopardy from Congressional cutbacks. On the drug importation issue, he defaulted to reciting familiar arguments about counterfeiting and improper storage. While these are serious potential problems, in the current political conversation these issues seem intended to deflect discussion about ways to cope with out-of-control drug prices. Recent

news articles about the diversion of HIV drugs from Florida to Texas via a string of small, shady pharmaceutical wholesalers makes it difficult to understand where the risk is in importing pharmaceuticals from state regulated distribution networks in Europe. Between the ill-regulated domestic drug channels and the hourly email offers I get for vicodin and valium, it seems disingenuous to suggest that the greater risk to consumers comes from abroad.

Debra Birkrant, director of the division of antivrial drug products, reviewed the various paths that drug approval can take. Accelerated approval for important new drugs to treat HIV will always be considered, she said, despite the demands placed on the agency to assure a thorough evaluation within the six-month window given to fast-tracked agents. She also had a request for the activists: instead of delivering a position paper outlining community concerns and unanswered questions at the end of the process, the agency would find it helpful to hear the activist analysis earlier on, so that it could help guide the agency's priorities.

After the meeting broke up, activist and FDA staffers mingled and exchanged ideas about how each could help the other assure that future HIV drugs were approved with fewer gaps in knowledge and better data on safety and effectiveness. It's clear that the people of the FDA are keenly interested in understanding everything about the world of AIDS and how the drugs they regulate are used in the real people's lives. In particular, it was gratifying to learn that several senior staffers who are physicians volunteer their time in local HIV clinics every week, helping them to keep in touch with the realities of HIV care.

The FDA workers we met clearly take their duties seriously; they should feel fortunate to work for an agency that exemplifies the highest ideals of what government can do. In proactively reaching out to the community for this meeting, the FDA and CDER went beyond what was expected and set a welcome tone for future cooperation. A follow up meeting with CDER's sister center, the Center for Biologics Evaluation and Research (CBER) is being planned. CBER will play an important role in the development of HIV vaccines as those candidates begin to enter clinical trials.

Guidelines Panel Responds

ATAC received another demonstration of the power of activist intervention in the recent revision of the HHS HIV/AIDS Treatment Guidelines. ATAC had sent a letter to John Bartlett and members of the guidelines panel asking that ambiguous links between d4T (stavudine, Zerit) and lipoatrophy in denoted Table 12a be strengthened.

The revisions also now clarify that the "preferred" classification attached to certain regimens is a general designation, and that one of the "alternative" regimens may actually be the preferred regimen for a selected patient depending on circumstances. This addresses activist concerns that the guidelines are sometimes mistaken as a "cookbook" for HIV care. Also, two recently approved drugs are now included in the guidelines. Atazanavir has been added as an alternative PI and FTC has been added as an alternative NRTI. Fosamprenavir was approved too recently to make it into this round of revisions.

The recent spectacular failure of tenofovir + abacavir + 3TC updates a section on regimens that should never be offered at any time. Another triple NRTI regimen, tenofovir + ddI + 3TC, also joins the "do not use" list, as does the combination of ddI and d4T in all cases; formerly the combo was only proscribed during pregnancy. Atazanavir plus indinavir are also now contraindicated due to their potential for worsening elevated bilirubin levels, and mixing 3TC and FTC is not recommended because they have such similar resistance profiles.

Finally, new data on using Fuzeon in patients with virologic failure has been added.

The guidelines are neccesarily a work in progress and the logistics of keeping up with changing treatment practices and new drug data is daunting. With these more frequent updates and the willingness to respond to community input, the guidelines are more than ever before becoming a "living document."

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Testimony on Accelerated Approval September 1994

By Carlton Hogan
(July 28, 1961–November 18, 2003)

In 1994, Carlton Hogan testified before an FDA Antiviral Advisory Committee about the risks of letting drugs loose in the population without a rigorous method to detect and report late emerging toxicity. In 2003, AIDS activists met with FDA and repeated many of the concerns that Hogan outlined: the need for post-marketing follow-up, the failure of drug companies to live up to commitments made to study drugs after they are approved, the inadequacy of penalties available to FDA for enforcing those commitments. Hogan's testimony seems especially prescient as it was made before the advent of truly effective antiretroviral therapy—and well before lipodystrophy and other complications associated with the new regimens had come to light. Carlton Hogan was an intellectual and moral leader in the AIDS treatment activist movement at a critical time and these excerpts from his testimony remain provocative today.

Access to promising new drugs is a right one cannot deny patients with a fatal illness. However, this right carries with it the responsibility to provide information that will advance science and help future generations of patients.

Despite the serious nature of my personal circumstances, I am loath to ingest any more potentially useless and toxic therapies. Poisoning myself seems an irrational response to a threat on my life. I think there is a very natural tendency to trust medicine in this age of antibiotics, and to believe a priori that taking "something" is always better than taking "nothing". While comforting, this notion is also quite incorrect.

The current accelerated approval regulations are adequate, albeit somewhat ambiguous, hence this meeting. One of the more important components, to my mind, is the provision for FDA to ask for further post-marketing (phase IV) studies if they have concerns as to the efficacy or safety of a drug receiving accelerated approval. Unfortunately this component, while reasonable in conception, has proved unworkable in execution. ddC received approval on the basis of little clinical information, conditional on Roche later making a determination of clinical efficacy. Of course as everyone in this room no doubt knows, Roche did not follow through, and those studies have not been done to date.

Unfortunately it appears that FDA's only recourse in such a situation would be to withdraw a drug from market, a politically difficult solution, and a cruel one as well, as persons taking ddC would be abruptly dropped. [The neurotoxicity of ddC subsequently became apparent and the drug, while still available, is now rarely used. Ed.] Clearly, in the absence of evidence of harm from ddC this would be an unacceptable solution, even were it politically possible. I think it is highly unlikely that we will see an HIV drug withdrawn from market unless it proves overwhelmingly toxic (and given AZT's toxicities, it is hard to imagine how bad that might be), or unless there is a replacement that is so clearly superior as to make much of this discussion moot. Therefore much of the requisite information will have to continue to be collected prior to full unrestricted approval.

It would be great if early testing of toxicity, such as occurs in Phase I trials, could be counted on to uncover all of a drug's deleterious effects. But some toxicities develop only in some persons, or only over longer periods of time. None of the phase I or II trials of AZT revealed the now widely recognized side effect of myopathy. It was only after large numbers of patients had taken AZT over long periods of time that myopathy became apparent. I believe it eminently possible, and even probable, that there are many compounds biologically active against HIV, which are able to clear short term toxicology testing, have a pronounced biological effect on the surrogate of your choice, yet in the long run do more harm than good. In the quest for an effective anti-HIV treatment, we are looking for something to interfere in intercellular processes. I fear that our biochemical "fingers" are still a little too thick and blunt to "fix" that finely machined watch without perturbing the system in unknown, and possibly untoward ways. And perhaps we may be a little too arrogant and insecure to admit the limitations of our knowledge and skill.