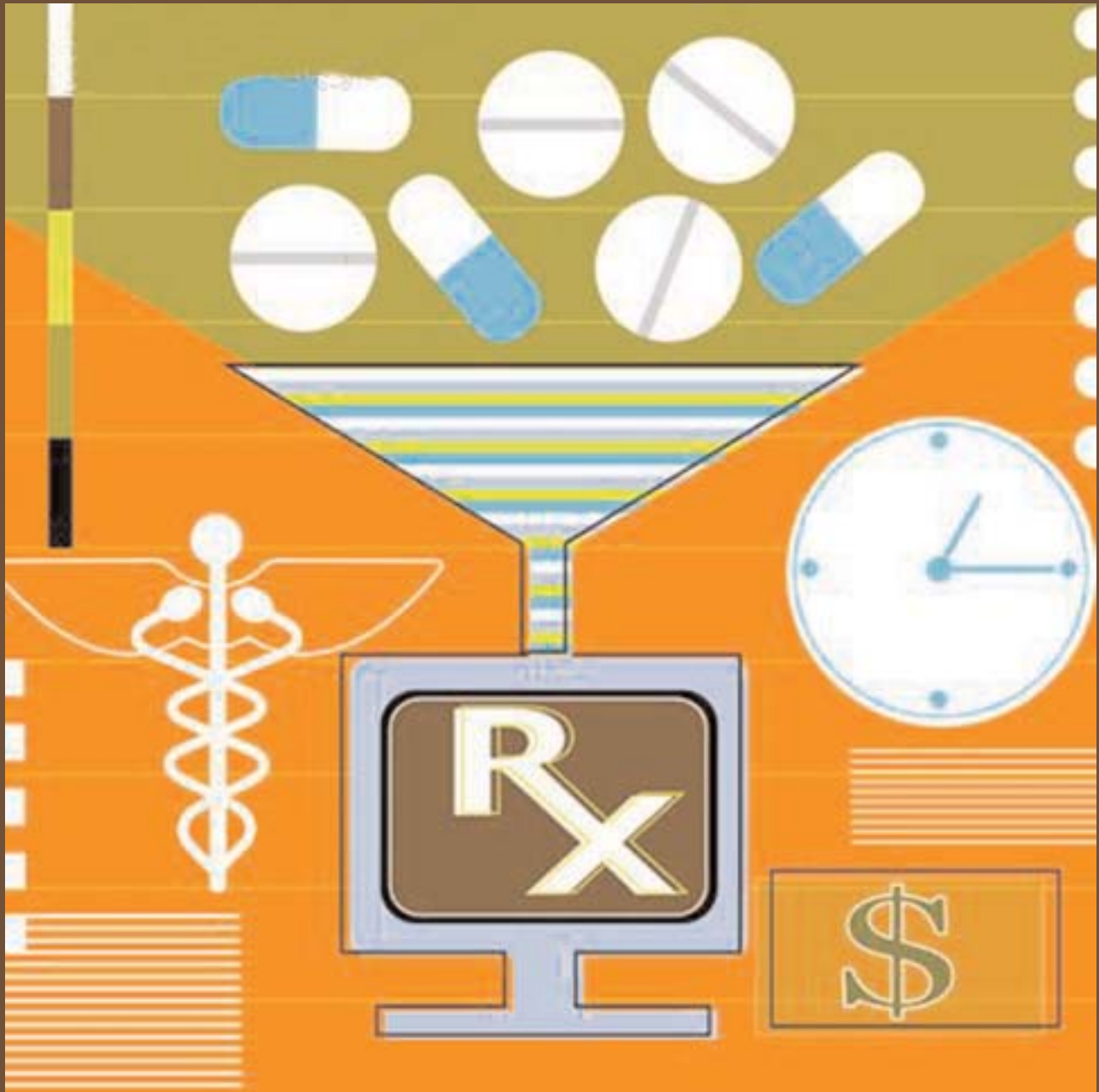


IAPAC

MONTHLY



Examining the **PHARMACO**Economics of US AIDS Drug Access

S3

From the President

José M. Zuniga

S4

Public Policy

Mark D. Wagner

S8

Why is IAPAC examining AIDS drug access in the United States?

José M. Zuniga

S10

An overview of AIDS drug access in the United States

Christine Lubinski

S15

Examining the pharmacoconomics of HIV treatment

Patrick G. Clay

S23

Untangling the economics of drug pricing

Joshua P. Cohen

S29

Defining the impact of AIDS drug pricing on the public sector

Lanny Cross

S34

Defining the impact of AIDS drug pricing on the private sector

Michael Allerton

S39

A physician's call to action

Benjamin Young



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Editor's Note: This *IAPAC Monthly* supplement features transcripts of presentations delivered at a one-day summit entitled, "Examining the PHARMACOEconomics of US AIDS Drug Access." The transcripts, which are accompanied by selected slides, were edited to conform to *IAPAC Monthly* style. Visit www.iapac.org to access complete slide sets.

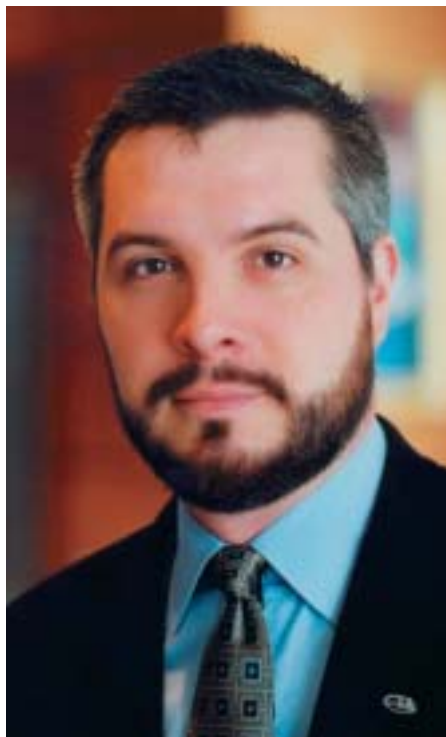
Challenging the status quo

José M. Zuniga

The International Association of Physicians in AIDS Care (IAPAC) secured almost 40 percent of our 2003 annual budget from pharmaceutical and diagnostic companies, through unrestricted educational grants, to advance third-party medical and patient education initiatives. Our other revenue sources include membership dues (individual and institutional), government and foundation grants, and private donations.

I describe our diversified funding sources in introducing this *IAPAC Monthly* supplement because it is often thought by some that accepting money from the pharmaceutical industry is akin to accepting to wear a muzzle. Not so. For as long as I have led IAPAC, this association has adhered to a principle of challenging the status quo (especially where it contributes to unnecessary suffering and hastened deaths), no matter the repercussion. And that principle has guided our advocacy efforts around AIDS drug access in resource-limited countries of the developing world.

The challenge in the United States today—although not equal in statistical proportion—is equal from the human perspective because, as of April 7, 2004, more than 1,200 people living with HIV/AIDS find themselves on AIDS Drug Assistance Program (ADAP) waiting lists nationwide. The system is buckling under two pressure points—not enough money, and high prescription drug prices. Thus IAPAC's first summit examining the pharmacoecconomics of AIDS drug access in the United States—a daylong gathering the association hosted last month



in Washington, DC, to discuss *both* the need for increased federal and state funding for ADAPs *and* the pressing need to address the contentious issue of AIDS drug pricing.

As Mark D. Wagner's summary article and the accompanying presenter transcripts will attest, IAPAC brought together a diverse group of individuals from various walks of life to engage in a very serious, and long overdue, dialogue around what may mushroom into a full-blown crisis of even greater proportions within months. I do not wish to reiterate the points made so eloquently by my fellow summit presenters, except to echo the call from IAPAC member and Colorado

physician, Benjamin Young, that this is a subject on which physicians and allied healthcare professionals cannot remain silent. Though they may fall outside the traditional clinical purview, public and fiscal policy decisions become the domain of medical professionals when they create barriers to fulfilling an oath to provide the best possible treatment for their patients. As Young put it, "physicians and other healthcare providers have the moral obligation to become involved in this issue."

Healthcare is a human right. IAPAC founding member Jonathan Mann argued that when that right is challenged, those of us who work to provide healthcare must act. I am proud to say that your association continues to keep that principle at the forefront of our activities. ■

José M. Zuniga is President/CEO of the International Association of Physicians in AIDS Care, and Editor-in-Chief of the IAPAC Monthly.



IAPAC hosts HIV pharmacoeconomics summit

Mark D. Wagner

In many respects, the frontline of the fight against HIV/AIDS left the economically wealthy countries of North America and Europe sometime around the mid- to late 1990s. Researchers had developed effective treatment in the form of antiretroviral therapy, and the governments of these wealthy nations were able to guarantee access to antiretroviral drugs as “essential medicines.” Morbidity and mortality decreased dramatically in countries such as the United States, and the most urgent goal for HIV medicine and AIDS advocacy became addressing the reprehensible global treatment gap that makes antiretroviral drugs unavailable to the millions who continue to die of AIDS-related illnesses in resource-poor countries.

However, given that there is neither a cure for AIDS nor a viable vaccine, and treatment remains an expensive, life-long endeavor, sustainability is vitally important to the world’s response. Where there has been success in providing antiretroviral therapy to patients, we must ask how well the commitment is being maintained. And, in the case of the United States, where HIV/AIDS was first detected and responded to, and which has been the site of most breakthrough research discoveries, the unfortunate answer is “poorly.”

As cited repeatedly during a day-long summit held April 6, 2004, in Washington, DC, entitled “Examining the PHARMACOEconomics of US AIDS Drug Access,” the latest estimates count approximately 800 HIV-positive patients on waiting lists to access HIV/AIDS care, including antiretroviral therapy, through various state AIDS Drug Assistance Programs (ADAPs), designed to provide

coverage for under- or uninsured Americans. At the summit, which was hosted by the International Association of Physicians in AIDS Care (IAPAC), clinicians, policy experts, patient advocates, pharmaceutical industry representatives, government officials, and other delegates who had gathered to discuss contentious issues around AIDS drug access generally agreed in predicting that this sobering statistic would increase. Indeed, the National Alliance of State and Territorial AIDS Directors (NASTAD) announced a day later its new estimate of the number of HIV-positive patients on ADAP waiting lists: over 1,200.

Patients are being made to wait for the antiretroviral therapy they need for reasons that tend to build on each other. Pharmaceutical companies are raising the prices of old agents, and charging unprecedented rates for new ones, even as government programs to provide treatment receive near flat, flat, or decreased funding from federal and many state governments.

These programs become responsible for more and more patients because antiretroviral therapy greatly increases life expectancy, but also because the same tight economic environment that makes it difficult for government to increase its spending means growing numbers of Americans are unable to afford private insurance that covers HIV treatment. Patients falling in and out of private insurance coverage, in addition to increasing HIV incidence among many Americans who have never been privately insured for healthcare, translates into an increased burden on an already strained government safety net.

These weaknesses are emblematic of a system cobbled together on the fly—one that has much to recommend it in its ability

to develop and provide antiretroviral therapy to thousands of Americans over the years, but that bespeaks, perhaps, an emphasis on quick responses over long-term planning.

There is great variation from one state to the next, confusion about which programs cover which patients, and a mountain of paperwork required to gain entrance to treatment programs. In one infamous irony, Medicaid, the system of federally funded state programs that pays for healthcare for Americans who are disabled and, in some states, below a certain income threshold, does not cover HIV-positive patients until they have an AIDS-defining illness. The ADAP was meant to fill this gap, covering patients who are living with HIV but who have not yet developed AIDS, but Medicaid often has better benefits and is a federally guaranteed entitlement. Despite overwhelming evidence that antiretroviral therapy is best started long before patients are symptomatic, they are sometimes asked, in essence, to get sicker before they are offered better coverage.

With regard to developing and selling medicines, a system that does not regulate drug prices, despite granting exclusive marketing rights to pharmaceutical companies, may be credited with establishing a research-friendly environment, and all summit presenters agreed that profit incentives had been effective catalysts for past drug development and would be needed in future. Many expressed fears, however, that absolute freedom to set prices was leading to costs that are too much for public and private payers to bear. This thorny dilemma is in many ways the same that is being debated about pricing of all pharmaceutical products in the United States, and that has come to a head over the issue of re-importation of



Craig Thompson, Executive Director of AIDS Project Los Angeles, shares his perspective on the impact current financial constraints are having on patient access to appropriate HIV/AIDS care and support services.

drugs, at price-controlled rates, from Canada, many European countries, and Mexico. Immediate AIDS-specific points of concern include Abbott Laboratories' 400 percent price increase of ritonavir (RTV), the high cost of Roche Laboratories' enfuvirtide (ENF), and a general pattern of increasing prices for new antiretroviral drugs entering the market.

In discussing and debating the best ways to address these growing concerns, the concept stressed by the experts gathered at IAPAC's summit was "balance." There must be a way for society to ensure access to drugs that mean the difference between life and death, even in a time of increased budget constraints. There must be a way to balance profitability, and, thus, continued research and development, with drug pricing that does not cause impossible strain on the system. As IAPAC President/CEO José M. Zuniga stated in his opening remarks, economic realities and ethical imperatives can, and must, co-exist.

Zuniga summed up the current state of HIV/AIDS treatment in the United States as "the best of times, and the worst of times." On the one hand, there are 19 US Food and Drug Administration (FDA)-approved antiretroviral agents, as well as three fixed-dose combinations. Death rates and AIDS diagnoses have fallen dramatically. Where 50,610 people with AIDS died in 1995, only 16,371 died in 2002.

One good example of the much-touted success of antiretroviral therapy came from Michael Allerton, HIV/AIDS Operations Policy Coordinator with

Kaiser Permanente's Permanente Medical Group. Among the nearly 15,000 patients living with HIV/AIDS who receive care from the giant health maintenance organization (HMO), the mortality rate has been less than 1 percent per year for the last six years. This figure "includes all fatalities, so some of those individuals were killed in car accidents or died of heart attacks," explained Allerton. Successful treatment can truly turn HIV/AIDS into a manageable chronic illness.

But increasingly physicians and allied healthcare professionals have to manage more than antiretroviral therapy. They have the difficult task of helping patients maintain healthcare coverage, and debating whether to begin therapy when coverage gaps might mean a break in treatment. Economic constraints are pressing into the ability of healthcare professionals to make decisions based on what they know is the ideal from a purely clinical standpoint.

This other side of the "best of times, and worst of times" divide is marked not only by the ADAP waiting lists, but by socioeconomic and epidemiological factors that are exacerbating the holes in what Christine Lubinski, Executive Director of the HIV Medicine Association (HIVMA), called "a fragmented patchwork of a healthcare system that links access to healthcare with employment, disability, age, sometimes poverty, and other factors" and which offers "no guarantee of continuity of care."

The list of entities that pay for AIDS drugs is a long one: Medicaid, private health insurance plans, ADAPs, Veterans

Administration (VA), US Department of Defense (DOD), Medicare, and a miscellaneous grouping of charities and other state funds. And, as Lubinski made clear, there is tremendous variability of coverage within most of these categories of payers. One state Medicaid plan or ADAP has more stringent eligibility requirements than another; some formularies of available drugs are very broad, others quite narrow. Although data are sparse on drug coverage through private insurance, there is no doubt that different plans offer vastly different coverage.

Allerton pointed out that the categories are not necessarily discrete in terms of how people living with HIV/AIDS receive healthcare coverage. Those who have private insurance that is insufficient may rely on ADAP for additional coverage, and that will probably be more and more the case as private insurance plans raise premiums, increase co-pays, and, particularly with regard to HIV/AIDS, impose caps on annual spending. Lubinski reported that Mutual of Omaha did just that (and defeated a lawsuit challenging the decision) in the late 1990s.

Many of the same cost-cutting measures are being implemented in government programs. Lanny Cross, who manages ADAP for the New York State Department of Health, told summit delegates that Medicaid and ADAPs in many states are limiting prescription refills, capping enrollment, and restricting the criteria for medical and financial eligibility. Lubinski reported that the new Medicare law, signed by US President George W. Bush in late 2003, means older people living with HIV/AIDS will be able to receive drug coverage from the entitlement for the first time. However, Lubinski pointed out that among other concerns, the coverage may not be better than what patients currently have, and rules require them to agree to a long-term plan before learning all the coverage details.

All of these programs are at the budgeting mercy of lawmakers. For example, ADAP has received relatively small percentage increases from the US Congress over the last several years—from approximately US\$714 million in fiscal year 2003 to US\$749 million in fiscal year 2004. About the same percentage increase is likely in fiscal year 2005, and it will not cover the estimated need. Medicaid, which is the largest single payer for

HIV/AIDS treatment, has more secure federal funding, but both programs are heavily dependent upon state budgets, which are currently in notoriously bad shape nationwide. Unlike the US Congress, many state legislatures are required to pass a balanced budget, putting further constraints on funding decisions.

The states that tend to do the worst at supplementing federal money are often small Western and Southern states. These receive less federal money to begin with, by virtue of their smaller HIV populations. They are often in budget crunches, either because of depressed economies or a conservative ethos that calls for keeping taxes low. Having a smaller HIV community also comes into play again because there is not the constituent lobbying power of states such as California or New York.

Apart from an inadequate supply of public money, the other strain on payers' budgets, which was a major focus of summit discussion, is the increasing amount that payers are paying for prescription drugs. As people with HIV/AIDS are living longer, and as antiretroviral therapy is becoming more expensive, the pharmaceutical portion of most payers' healthcare budgets is straining. Allerton reported that although people living with HIV/AIDS make up less than 1 percent of Kaiser Permanente's total patient population, they account for the second highest total pharmacy costs. (Patients treated for depression make up the highest cost.)

As one presenter noted, however, these costs may need to be put into some perspective. Tufts University's Joshua P. Cohen, who is a Senior Research Fellow at the university's Center for the Study of Drug Development, argued that pharmaceuticals, not just for HIV/AIDS, but in general, are in many ways a bargain because they represent a much smaller cost burden than that of hospitalization and other healthcare services. According to Cohen, although costs for prescription drugs have risen as a percentage of what private and public third-party payers spend, they represent only 9 percent of the total healthcare expenditure in the United States. Patrick G. Clay of the University of Missouri and the Kansas City Free Health Clinic presented data showing the positive cost/benefit trade-off for antiretroviral therapy, stating that one hospital stay for the common opportunistic

infection *Pneumocystis carinii* pneumonia costs more than a year's worth of antiretroviral drugs.

As Cross pointed out, however, those savings are sometimes missed by a system such as ADAP, which essentially only covers the cost of drugs. There are no offset hospital costs, at least not visible ones, and the appearance to lawmakers may be only of consistently growing expenses as more patients are entering and utilizing the system *and* living longer.

There was general agreement, as well, that increasing numbers of patients covered each year cannot alone account for the unmanageable costs experienced by third-party payers. The high and increasing price of antiretroviral drugs is also a factor. Even if the use of those drugs eliminates the theoretical cost that would have to be paid for hospital visits if those drugs did not exist, that does not mean that any price, or price increase, is reasonable. Cross presented data showing a jump in pricing that began with efavirenz (EFV) in 1998 and continued through five of the next six new antiretroviral drugs. Abacavir (ABC), tenofovir (TDF), ENF, atazanavir (ATV), and fosamprenavir (FPV) are all priced near or above the higher price point established by EFV. Other agents, such as azidothymidine (AZT), the first FDA-approved antiretroviral drug, have undergone steady price increases that are greater than would be required to compensate for inflation. These price increases have real effects on access. Even when price increases are accompanied by industry-sponsored compassionate access plans for people receiving government aid, Allerton said, the strain is felt throughout the system because private insurance plans raise their rates to compensate, forcing more people into already over-burdened public healthcare plans.

It is important to note that all those prices are averages. An additional problem is the fact that no two buyers actually pay the same price for a given drug. Instead, they each work out their own private agreements with the various pharmaceutical companies, some getting much better deals than others, no one knowing what anybody else is paying. Imperfect information is known by economists to create market inefficiencies, and the pharmaceuticals market is no exception. When pricing data do become available, they reveal some rather backward results. For

example, in a 2001 study, Medicaid—again, the largest single buyer of antiretroviral drugs—was found to pay 33 percent more on average for antiretroviral drugs than other federal programs, Lubinski said. And there is variance within the Medicaid system, with Georgia paying the highest prices of the 10 states with the most HIV cases, while Massachusetts pays the lowest prices. In general, patients without any coverage at all, who have no one to bargain on their behalf, pay the highest prices for prescription drugs.

Another arcane process is the internal debate that pharmaceutical companies hold regarding what they should set as their average wholesale price (AWP), the “list price” that becomes the starting point for negotiations with different buyers. How do companies decide what to charge? How does that price relate to research expenses, marketing expenses, and overall profits? The generally touted figure of US\$800 million that is estimated for a company to bring a new drug to market from point of conception to research and development through clinical trials, remains a matter of much controversy. Although several pharmaceutical industry representatives attended the IAPAC summit, most said they could not speak to these questions, citing federal regulations designed to prevent collusion by prohibiting companies from discussing their pricing decisions.

During discussion, a consultant who works closely with an antiretroviral drug manufacturer—he asked not to be identified—described the pricing process. He portrayed it as an internal debate between such factions as the marketing team, whose goal is to maximize profits, and the public affairs team, which often seeks to guard against the company receiving a “black eye” for raising prices to a level that the patient and provider communities will view as unfair.

In his book, “Elements of Pharmaceutical Pricing,” EM Kolassa, an acknowledged pricing expert and frequent industry consultant, also emphasizes that pricing negotiations hinge on perceptions. He essentially argues that prices should be set at the highest possible level that will not instigate public backlash, taking into consideration the likelihood that affected groups are willing and able to act on their indignation. Setting prices based on costs is singled out as a very bad way to proceed.

Instead, Kolassa urges decision-makers to think about such factors as who actually pays for a type of drug, saying that if patients are usually covered by public or private payers, so they do not see costs themselves, the pharmaceutical company should charge more. He points to research showing that high prices for drugs treating certain types of indications are more likely to incur patient ire than are others, saying that acute illness and highly symptomatic chronic illness leave the most room for high prices. Other considerations are company needs, competition, and the company's preparedness to defend a high price against attack or promote the benefits of a low price. According to Kolassa, surrounding and superceding all these considerations is public policy.

"In the foreseeable future, a company must consider the responses and actions of government officials and patient advocates when setting a price," he writes.

In light of all that, it would seem that advocacy and working with the pharmaceutical industry to make companies aware of problems and concerns is becoming very important. Indeed, Zuniga and Allerton, among other presenters and delegates, specifically called for more and greater communication and activism, making clear that higher prices have real effects on the viability of the system and, therefore, people's lives.

Such efforts, however, are often frustrating. Some advocates who participated in what might be the most ambitious efforts to work with industry around pricing of AIDS drugs—the ADAP Crisis Task Force and the Fair Pricing Coalition—attended the summit and reported mixed results. The task force has been the more successful of the two, bringing together state ADAP or AIDS directors from 10 large states to negotiate ADAP-specific discounts for all ADAPs, and saving an estimated US\$60-65 million in the first round, Cross reported.

The coalition's efforts to establish lower overall prices, however, have not been very effective. Comprised of treatment advocates and government healthcare officials, the coalition attempts to work with pharmaceutical industry senior managers on pricing decisions. They emphasize the need for lower initial prices of new drugs and price freezes for existing drugs. Cross and Lei Chou of the AIDS Treatment Advocacy Coalition

(ATAC) reported that their efforts were largely unsuccessful. They had multiple meetings with decision makers and presented their data, but the companies, with some variance from one to the next, continued to bring in new drugs at or above existing price points and either refused or quickly reversed price freezes for older drugs. Chou said he felt "deceived."

The industry consultant, who, on condition of anonymity, described the pricing decision process, said that a company often does not see the multiplied effect of price increases. Raising the price of their one drug by 6 percent seems insignificant, but when all companies are acting similarly, it can have a tremendous market impact. The companies simply do not recognize the overall effect, he said, positing that antitrust laws preventing companies from discussing pricing in each other's presence might play a role in that myopia.

Even if companies do see the impact of their pricing decisions, of course, they are under no obligation to act accordingly. They are given the ultimate power to decide how maximizing profits will be balanced against setting prices to facilitate accessibility. According to Kolassa, "In healthcare markets, we are granted the unique authority, by virtue of the products that are developed, to charge whatever we wish... We have the peculiar ability to say to a patient, 'It's your money or your life.'" Even provided that industry takes that responsibility seriously, and strives for pricing that does not create barriers to access, as Kolassa goes on to suggest, there is no official oversight.

The traditional argument is that any attempt to tinker with industry's ability to set its own prices will result in reduced profitability and, thus, less of the research and development that is a benefit to everyone. There was general agreement at the summit that profits must be ensured as an incentive for research. Perhaps, however, it would be wrong to take for granted that any outside pricing intervention would cripple the industry. According to a Henry J. Kaiser Family Foundation study, average profits for pharmaceutical companies from 1994-2001 were 17.2 percent, by far the highest of any legal industry, and considerably greater than the 4.6 percent that was the average for all *Fortune* 500 companies. Warnings of an end to research and development due to past regulation

such as 1984's Hatch-Waxman Act (which effectively created the generics market) and 1990's Omnibus Budget Reconciliation Act or "OBRA 90," (which attempted to reduce Medicaid expenses) proved unfounded. Data from *Fortune* magazine, in fact, reveal that net profit as a percentage of sales actually increased rather dramatically in the years immediately following those regulatory changes, and they have not fallen off since.

Although time constraints for the first of several fora IAPAC intends to convene on this topic did not allow for many specific suggestions for reforming the pricing process, there was a sense among presenters and most delegates that the time for doing something along those lines might be upon us. It was also generally agreed that reforms should be broadly conceived in terms of both their impact and the actors involved in creating them.

Zuniga suggested a "mixed basket" of solutions, including industry profit concessions, but also review and amendment of the prescription drug system as a whole, increased federal and state ADAP funding, and increased attention to keeping people living with HIV/AIDS in private insurance plans. Benjamin Young, a physician with the University of Colorado Health Sciences Center and an IAPAC member, has been an outspoken critic of recent industry pricing decisions. He echoed the need for inclusive decision making in a "Call to Action" he delivered to end the summit.

Access to life-saving care must be recognized as a human right, Young said. And, though access to profits might also be a type of universal right, it is one that should be balanced against the greater human mandate to save lives. He called for an "unprecedented collaboration" between government, patients, advocates, physicians, allied healthcare workers, and industry to re-think all current operating procedures and inject a greater sense of ethics and community responsibility into every decision. He suggested this simple litmus test for policy decisions: "Are the strategies that you are developing consistent with how you would take care of your grandmother?" If the answer is no, Young said, those strategies should be changed. ■

Mark D. Wagner is Director of Communications at the International Association of Physicians in AIDS Care.

Why is IAPAC examining AIDS drug access in the United States?



José M. Zuniga

On behalf of the International Association of Physicians in AIDS Care (IAPAC), I would like to welcome each of you to our association's first summit on the issue of AIDS drug access in the United States. The summit will examine public and private sector provision of HIV/AIDS care, specifically antiretroviral therapy, as well as the issue of drug pricing.

We live in one of the best of times with regard to access to antiretroviral therapy; with 19 US Food and Drug Administration (FDA)-approved antiretroviral drugs and three fixed-dose combinations. We know that highly active antiretroviral therapy (HAART) has led to dramatic declines in

AIDS-related mortality. In fact, where 50,000-plus individuals died of AIDS-related causes in 1995, we witnessed a steep decrease to 16,000-plus deaths in 2002—and we know that this “miracle” is a direct result of HAART.

Regrettably, this is also among the worst of times in that an expanding antiretroviral drug armamentarium, while providing choices to patients and their care providers, creates an incredible financial strain on those systems that currently exist to guarantee access to people living with HIV/AIDS, especially the medically indigent. There are serious concerns about the additional expense of and about the price points for antiretroviral drugs at various stages of development, including Boehringer Ingelheim's new protease inhibitor, tipranavir (TPV). This at a time

when a growing number of Americans living with HIV/AIDS find themselves on waiting lists for AIDS Drug Assistance Programs (ADAPs) because of state and federal budget shortfalls, or must deal with one or more drastic restrictions in access to life-saving medications through their state ADAPs. And this is all compounded by sobering statistics telling us of increased HIV prevalence among un- and under-insured Americans.

Lanny Cross, Program Manager of New York State's ADAP, will speak about his experience in these difficult times. The 50-state ADAP network currently serves approximately 89,000 individuals who are low income, un- or under-insured, and non-Medicaid eligible. As of January 30, 2004, nine states had ADAP waiting lists with almost 800 people on those lists. Six

other states had implemented some type of restriction. According to recent modeling estimates, we know that a minimum increase of US\$217 million is needed in fiscal year 2005 to support state ADAPs nationally; US\$121.7 million of that is needed immediately to address accumulated funding shortfalls over several years.

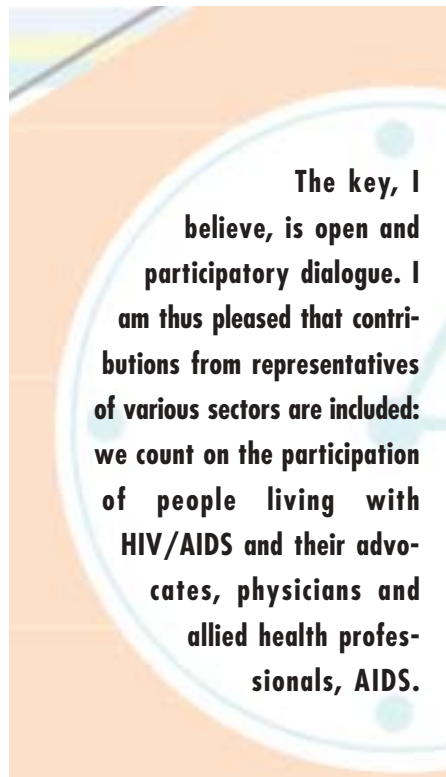
The private sector is also feeling a financial squeeze, what with a significant per capita growth in prescription drug spending. Michael Allerton, HIV Operations Policy Coordinator of the Permanente Medical Group at Kaiser Permanente will explain the already existing and soon-to-come restrictions on private sector AIDS drug coverage, to include formulary restrictions, prior authorizations, and multi-tier co-pay arrangements.

This one-day summit is meant to address both the economics and the ethics of AIDS drug access. Because IAPAC infuses all of its meetings with ethics, the necessary balance of economics and ethics around this public health challenge will be examined. On the economic side, the cost of prescription drugs is reflective of the need to recapture research and development (R&D) investment, and that argument will be presented by Joshua Cohen, Senior Research Fellow at the Tufts Center for the Study of Drug Development. He will also demonstrate in cold, hard numbers another economic reality: that the public and private sector actors charged with guaranteeing AIDS drug access are struggling to keep pace with demand. On the ethical side, I am certain that our discussions will reinforce the notion that, for example, drug pricing decisions must be made within the context of a moral duty to assist those in need. Our obligation is to provide more than succor to people living with HIV/AIDS, especially because we know beyond a reasonable doubt that early HIV treatment saves both lives and money. It is thus necessary to provide such treatment universally through various mechanisms, including the Early Treatment for HIV/AIDS Act (ETHA) currently before the US Congress.

This summit is not about blaming the pharmaceutical industry for the entirety of the problem. Certainly drug pricing is a concern. But there is an additional need for increased funding from federal and state governments. Increased collective price negotiations efforts are critical, as is

a broader systems approach to prescription drug access and funding. And, obviously, thought needs to be given to regulation through reference pricing and the enhancement of cost relocation schemes such as the ETHA.

A dose of reality is necessary in everything that we are addressing today. The business of manufacturing pharmaceuticals is based on a free-market system, and profitability remains a key incentive. But, we need to look at a mixed basket of solutions if we are to make any progress in an era when we are experiencing severe economic constraints on both the public and private sectors. Thus, industry profit concessions, prescription drug system reviews and amendments, increased but targeted federal and state ADAP funding, and increased attention to private insurance coverage must be on the table as we cobble together our strategy to maintain and expand AIDS drug access in the United States.



The key, I believe, is open and participatory dialogue. I am thus pleased that contributions from representatives of various sectors are included: we count on the participation of people living with HIV/AIDS and their advocates, physicians and allied health professionals, AIDS service organizations, government officials, insurance company decision-makers, and pharmaceutical company representatives.

Why the mixed basket approach to arriving at solutions? Because we need to ensure the sustainability of our efforts to guarantee AIDS drug access to Americans living with HIV disease. This is an argument IAPAC is advancing on several different fronts as we attempt to expand access to antiretroviral therapy in the developing world. It is no less important here in the United States, especially in light of the cruel reality that there are hundreds—and there may soon be thousands—of people living with HIV/AIDS in this country who today do not have access to life-saving and -enhancing antiretroviral therapy.

Christine Lubinski, Executive Director of the HIV Medicine Association (HIVMA), provides an overview of AIDS drug access in the United States. My hope is that her presentation will provide a framework from which we can derive context for an examination of the pharmacoeconomics of HIV treatment—which is covered in a presentation by Patrick Clay, Assistant Professor of Medicine in the Division of Pharmacy Practice at the University of Missouri-Kansas City. And, to keep us focused on what our advocacy is all about—the care of men, women, and children living with HIV/AIDS—we are pleased to count on the participation of Benjamin Young, an IAPAC physician member and Clinical Instructor in the Department of Medicine at the University of Colorado Health Sciences Center. He will deliver IAPAC's call to action around AIDS drug access.

Our ultimate objective is to develop some recommendations for advancing a far-reaching advocacy and legislative agenda to expand AIDS drug access in the United States, as well as strategies for public and private sector influence on AIDS drug pricing; again, with an eye toward the future. There are certainly contentious issues with which we have dealt in recent months and which merit discussion, specifically Abbott Laboratories' decision to implement a 400 percent price increase for its protease inhibitor, ritonavir (RTV). Yet, I am hopeful that today's summit will include a healthy dose of forward thinking aimed at securing the future of AIDS drug access in the United States. ■

José M. Zuniga is President/CEO of the International Association of Physicians in AIDS Care.

An overview of AIDS drug access in the United States



Christine Lubinski

A couple of disclaimers: One, I know very little about drug pricing. Most of my work in AIDS has been about healthcare access, which means I know a little bit about the programs that pay for drugs. So, basically, what I am going to do is give you a very quick overview of who pays for drugs in the United States.

These are the major providers of payment for AIDS drugs: Medicaid; private health insurance; the Ryan White CARE Act, including but not limited to the AIDS Drug Assistance Program (ADAP); the Veterans Administration (VA); the US Department of Defense (DOD);

Medicare; and uncompensated or charity care. I am not going to talk about the DOD. They are doing very well indeed financially, and have fabulous coverage. But, just moving through some of these programs, I think the first thing to say is—and, I guess, as I was preparing this presentation I sort of stepped out of being an American and thought—what an outrageous situation we continue to deal with here in the United States.

We have, in fact, growing numbers of people who are uninsured, 43.6 million in 2002, and still no comprehensive solution to this problem. Looking first at the private health insurance market, which may cover about a third of the people in this country:

- Premiums have risen 13.9 percent.

- Co-pays are going up. The average co-pays are US\$9 for generics, US\$19 for preferred drugs, and US\$29 for non-preferred. Theoretically, most of the antiretrovirals would be preferred drugs because there are no generic substitutes.
- 71 percent of workers are in plans that use a formulary.
- US courts have upheld coverage limits for the treatment of HIV/AIDS related to private health insurance. Several of us worked on and supported an *amicus* brief a couple of years ago when Mutual of Omaha had policies that capped spending for HIV care at a very low level. The US Supreme Court did not grant cert. So, of course, one of the concerns is whether we are going to begin to see more of these coverage limits.

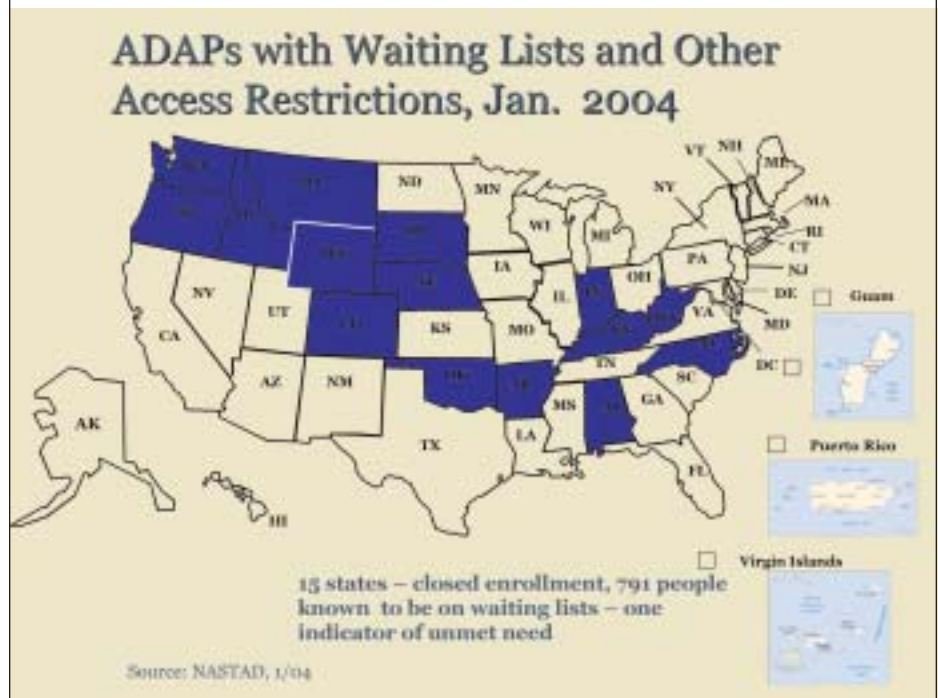
There are also very little data. As mentioned by José [M. Zuniga] in his opening remarks, more attention should be paid to the private health insurance market. There are really very little data on what is happening with AIDS care in that market, although there are probably snapshots of what is happening in some parts.

Medicaid is the largest payer of AIDS care and the largest payer of AIDS drugs. In 2003, Medicaid spent US\$8.5 billion for more than 200,000 people. It is important to note that eligibility requirements include being a member of a specific category, as well as being poor. This is not a universal access program for poor people. Most people with HIV/AIDS qualify on the basis of disability or as a caretaker parent of poor children. The eligibility issues have been huge, especially since the advent of highly active antiretroviral therapy (HAART), and clearly there is an urgent need to get people access before they become completely disabled by AIDS, especially since we know that drug intervention after an AIDS diagnosis has a poorer prognosis than intervention before a diagnosis. But states are required under federal law to cover medically accepted indications of US Food and Drug Administration (FDA)-approved drugs and off-label use.

Just as the rest of our economy, Medicaid is in a huge financial crisis. What we have seen is a number of cost-control measures on prescription drug access, everything from preferred drug lists to preauthorization, to requiring generics, to increasing co-pays, to locking individuals in to get their drugs only at one pharmacy, and generally tighter controls on high-cost drugs. Probably the most worrisome of all the cost-control measures is the increasing number of states that are actually limiting the number of prescriptions that people can get filled per month.

One of the other cost containment strategies is reduction in acquisition costs. The states are trying to get greater discounts on average wholesale prices (AWPs) for drugs in their formularies, limits on the number of medications, limits on the number of refills, etc. There are certainly states, including the states of California and Florida, both of which are among the top three states in terms of numbers of people with HIV/AIDS, that are looking to dramatically increase co-pays for certain populations of people on

Slide 1.



Medicaid, and obviously with the number of prescriptions people with HIV/AIDS need to fill, this could really be a barrier to getting everything they need.

Many of us have been working for some years on the Early Treatment for HIV Act (ETHA), which is about addressing the need for early intervention in healthcare. It gives states the option to amend their Medicaid eligibility, basically to extend Medicaid to low-income people with HIV before they become disabled. It also gives states an enhanced federal match to do so, modeled on the Breast and Cervical Cancer Act. We have spent a lot of the last two years defending the Medicaid program, but also feel it is important to have a proactive strategy, and to acknowledge the ways in which Medicaid does not work for our population.

I want to give you a little bit of data on Medicaid prescription drug prices. The latest estimate is from fiscal year 1999, which is obviously a long time ago, but Medicaid spent US\$617 million on anti-retroviral drugs, and what has been discovered is that, notwithstanding the language about Medicaid getting the best price on prescriptions, in fact, that program categorically does not get the best price. A study specifically on AIDS drugs found that Medicaid pays 33 percent more than other federal drug discount programs for HIV drugs, including a number of

ADAPs. There is also wide variation in the prices paid for the same drugs among state Medicaid agencies in that particular study, which looked at the 10 states with the highest number of cases. Massachusetts paid far less than any other state, and Georgia paid far more. In all the discussions we have been having over the last couple of years about the South and the southern epidemic and the number of people on rural Georgia's ADAP waiting lists, it is sort of interesting to find out that Georgia is actually getting a pretty bad deal on Medicaid prices.

All 50 states and the US territories have ADAPs. The goal of the program is to provide HIV/AIDS-related drugs to uninsured and underinsured persons. Funding is based on formula, and is largely federal. There is some state funding, but the amount of state funding varies quite dramatically. The overwhelming majority of the money, and this has consistently been the case since 1997 or 1998, is spent on antiretroviral drugs. The majority of recipients are people who would qualify as low-income. Ten states account for more than three quarters of all the expenditures for drugs. It is a discretionary program; how well we know that. Funding depends on annual congressional appropriations. Such decisions lately have not been in our favor, and there is little indication that that situation is going to change. I cannot remember the

last time we had a successful supplemental funding approach for ADAP—the payer of last resort, intended to fill in the gaps in Medicaid and private coverage, because the private health insurance market has been pretty successful in avoiding paying for our population of people, by and large.

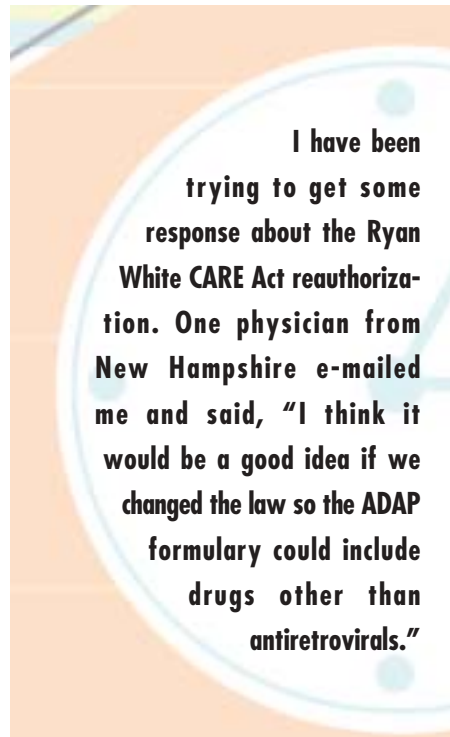
The ADAP is critical. It is certainly a major focus of our community. A lot of ADAPs have been imposing cost-containment strategies, enrollment caps, waiting lists, restricted access to drugs, and per capita expenditure caps. They are only going to pay for X thousand dollars per year per beneficiary, by implementing limited formularies and reducing financial eligibility criteria—though, by and large, that does not save a lot of money because there are not very many people on the higher end of eligibility. This is a map indicating where ADAP restrictions are the most serious (Slide 1). According to the National Alliance of State and Territorial AIDS Directors (NASTAD), there are 791 people currently on ADAP waiting lists.

We are clearly having challenges in terms of providing access to drugs. I think this is also a time when most people in the world, with the attention garnered by the global epidemic in the last few years, assume that there is universal access to life-saving drugs in the United States. As you all probably know, there is a lot of variability in ADAP eligibility. What drugs are on the formulary? How much do states contribute? That is determined by individual states, it varies pretty dramatically in terms of financial eligibility. There are no minimum formularies or requirements by the federal government, and there is a lot of discussion every time we talk about Ryan White CARE Act reauthorization about whether there should be. I think the most common view is that the only way this can happen is if there is some type of federal responsibility for helping to implement that formulary state by state. There are dramatic differences: 18 drugs versus 463 drugs.

I represent HIV physicians now, and I have been trying to get some response about the Ryan White CARE Act reauthorization. One physician from New Hampshire e-mailed me and said, “I think it would be a good idea if we changed the law so the ADAP formulary could include drugs other than antiretrovirals.” Has he been to New York lately? Their idea of a cut in the formulary is to reduce the amount

of Ambien® people can get per month. People tend to think the ADAP that exists in their state is the same as programs in every other state.

Not all ADAPs receive state contributions, and although 36 states contributed in 2002, that was two fewer states than contributed in 2001. There is a tremendous variability in negotiated prices among state ADAPs. There have been some precedents in recent years of negotiations between ADAPs and individual pharmaceutical manufacturers; they have led to some



agreements, although some people tell me that several of the companies have reneged on those agreements already. About half the states get 340B drug discount prices that are available to some public health entities. In order to do so, you have to acquire drugs through a central purchaser. The other half have a rebate option that allows them to access Medicaid rebates on a quarterly basis.

I think we often forget about one of the biggest providers of HIV care: the VA. In fiscal year 2003, the VA provided antiretroviral drugs to almost 15,000 people and had over 19,000 people with HIV/AIDS under its care. The VA exists in a rarified environment where drugs are purchased through one of the only statutorily discounted price programs enacted by the federal government. The prices are called “Federal Ceiling Prices” and they are part of the Federal Supply Schedule, which is

also how federal contractors get a good deal on buying commodities such as office equipment. These prices, which are dramatically lower than what Medicaid and most ADAPs get, are available only to the VA, DOD, US Coast Guard, and some elements of the US Public Health Service (PHS).

In 1997, some of the national AIDS groups joined forces with the National Association of Public Hospitals and tried to enact legislation that would allow ADAPs to access the Federal Supply Schedule, because public hospitals were hemorrhaging financially from the high cost of AIDS drugs. I never saw such a quick reaction from the pharmaceutical industry in my life. Within days the word was out that the AIDS community was trying to undermine medical care for veterans, which I thought was a sort of interesting take on all of this.

Moving on to Medicare, which before last year would have been a very short conversation, since Medicare currently pays pretty much exclusively for inpatient drugs and for some outpatient cancer medications. We have a new Medicare prescription drug law, which is a very complicated piece of legislation in its own right; but briefly, starting this spring and next year beneficiaries will have access to Medicare-endorsed discount drug cards, and US\$600 in an annual drug subsidy will be available for low-income seniors and persons with disabilities, which will indeed include some people with HIV/AIDS. In 2006, beneficiaries will have a choice of staying in fee-for-service Medicare with access to private drug-only plans, (emphasis on “private”) or Medicare Advantage (MA) integrated plans that are essentially Medicare-managed care plans that also include drugs, but there will be preferred provider organizations (PPOs) as well as health maintenance organizations (HMOs) in that option.

There will be reasonably generous subsidies to help low-income beneficiaries pay premiums, and cost sharing. Our community was a very small part of a very large debate, but we did try to do some advocacy around issues that would be critical. We do not really know the number of people with AIDS on Medicare, but speculation is that there are as many as 60,000 to 80,000 of them, and many of them are duly eligible for Medicaid but some are not, and in some states they are

a rather significant part of the ADAP rolls. I remember several years ago hearing a presentation by the ADAP Director for the State of Washington in which he stated that 15 percent to 17 percent of his state's ADAP rolls were people on Medicare only. So certainly this benefit has the promise of alleviating some of the burden on ADAP.

One of the very interesting parts of the Medicare prescription drug law is that we have a completely decentralized private-sector model, in which individual plans negotiate with pharmaceutical companies for prices. There is an explicit statutory prohibition against the federal government negotiating drug prices on behalf of 40 million Medicare beneficiaries. You would think that might get us a good deal. The pharmaceutical industry, which actually had historically opposed a prescription drug benefit from Medicare because they thought it would inevitably lead to price controls, in fact was incredibly successful—the big winners. They gained a large market with no threat of price controls, with all due respect to my friends from industry.

What about the Medicare law and people with AIDS? We have a number of concerns about this law... with which we are working administratively and perhaps someday legislatively to remedy. There is little hope that this law will be opened up legislatively this year. We are worried about comprehensive coverage of antiretroviral drugs on plan formularies. Not only can US Secretary of Health and Human Services (HHS) Tommy Thompson not negotiate prices, but his department cannot be proscriptive in terms of a formulary—it cannot say, “You must cover all antiretroviral drugs in all three classes,” for example. As we know, given the history of many people with this disease, all the options need to be on the table because there is no one-size-fits-all antiretroviral combination.

We would really like to change the law to allow Medicaid to supplement Medicare coverage with federal matching funds. Currently, people who are eligible for both Medicare and Medicaid must join this drug plan and if the drug plan does not have all the drugs they need, Medicaid will not be able to supplement their coverage. Their best hope will be to turn to the already-strapped ADAP in their community and ask for help, and it remains to be seen whether that help will be available. There

are some consumer protection issues that we are concerned about, which we actually share with many other constituencies. Right now Medicare does not have to provide even appeals information on enrollment, and they also require a beneficiary to file his or her own grievance, though under current Medicare law, for instance for the Medicare-managed care plans, a physician can file on behalf of a beneficiary, a friend, or a family member. We have beneficiaries who frankly are not equipped to negotiate a grievance process alone, so it would appear that in fact the statute has a way of discouraging people from filing grievances.

It is unclear whether ADAP can wrap around this benefit, and that is also one of the issues we are working on now. Virtually the only programs that can do so are the so-called “State Pharmacy Assistance Programs.” Our patients are not included under that rubric, but we are trying to argue that in fact, ADAPs are State Pharmacy Assistance Programs.

It is really important that all medically necessary drugs count toward the catastrophic limit. If you know anything about this law, you know that there is a phenomenon called a “donut.” It is about US\$2,000 that you are stuck carrying by yourself, unless you are categorized as low-income. But there is also a catastrophic limit over which you pay nothing, and one of our questions is: “If you have to buy drugs yourself that are not on the plan formulary, do those count toward the catastrophic limit or not?” Obviously, we know that drug costs to people with AIDS are going to facilitate them reaching that limit, and the sooner they do that and have federal support, the better off people will be.

Finally, there is the bizarre situation where the burden of health plans to provide information to the public does not begin until people actually enroll. If you are living in a community that has a fairly robust provider system with several plans, you cannot go to Plan A and ask, “What drugs do you cover?” They are not required to tell you. But as soon as you join a plan, you are locked in for a year. We think this is a little troubling, and this is actually one of the issues we hope to talk to HHS about, and hope there might be some wiggle room in regard to regulation. So, not only did the pharmaceutical industry win, but also the health plans won big with the new Medicare law.

There are many issues and challenges... A lot of people think the Medicare benefits start immediately. When deciding whether to enroll, a large number of Medicare beneficiaries have access to some private supplemental insurance that they hope to keep. There is a lot of concern that some of the companies that provide insurance for retirees and people with disabilities will in fact no longer do so. I am worried about my mother in this regard.

There are financial penalties for delayed enrollments. You have got to be informed about what to do, and if it is the best bet—for instance, making sure you get in the low-income subsidy program if you are eligible, which is pretty critical. How do you sign up? These are all things that I think people on the ground, Ryan White CARE Act-funded case managers and others, are going to have to help people do—for example, comparing plans and deciding which to join, because they are all going to be different. First of all, we are fighting for the right to make informed decisions about comparing plans, which we do not have; again, with the risk of consequences of bad decisions or a lock-in to a sub-optimal plan. It appears that the burden may be on the beneficiaries to track out-of-pocket cost. If you manage your finances the way I do, you would be in a lot of trouble that way. Obviously people with AIDS have a lot more challenges in their lives than I do.

Just some summary comments: We have, in case it is not incredibly obvious, a fragmented patchwork of a healthcare system that links access to healthcare with employment, disability, age, sometimes poverty, and other factors. Because of the categorical nature of access, there are no guarantees of continuity of care from childhood to old age in this country. There is no human right to healthcare. There is no legal right to healthcare, and obviously that has tremendous implications for access to drugs. Drug costs vary considerably across public and private programs by kind of system and by geography, like everything else related to the AIDS epidemic. The high costs of prescription drugs affect individual decisions to adhere to drug protocols, and also affect the capacity of public programs to offer a medication safety net. If drugs did not cost so much, ADAPs could offer more of them to more people, for example.

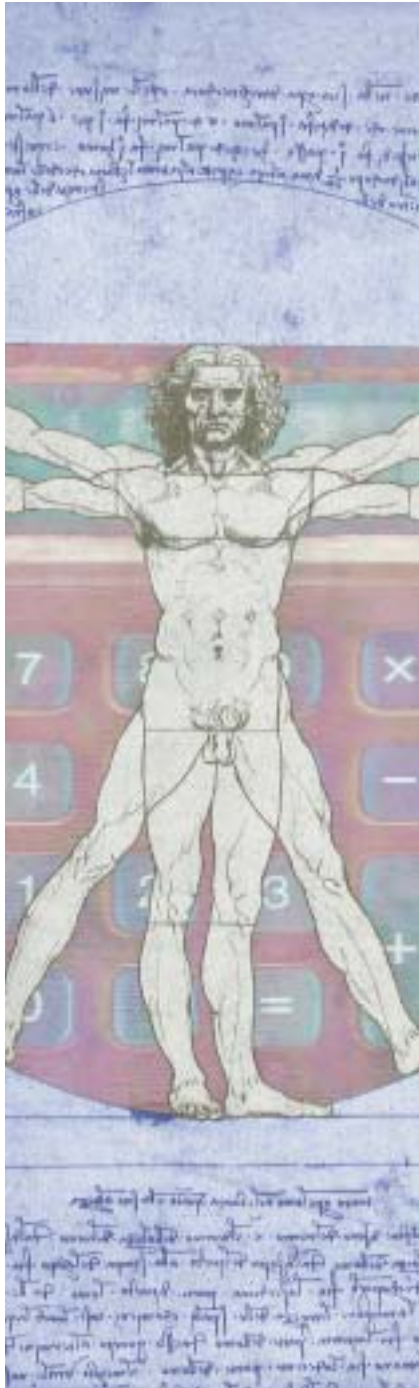
Most information about drug pricing is proprietary, even among state Medicaid programs and ADAPs, so they are not allowed to share information about that. So only the individual pharmaceutical companies have the big picture about what the pricing structure looks like across payers, and they only have that picture for their drugs. It is not a transparent process. It is very difficult to change. Patient-assistance programs sponsored by pharmaceutical companies serve a critical role as safety

nets for individuals, as eligibility for programs fluctuates or as benefits fluctuate, but they create tremendous burdens for providers and patients alike. I talked to one of our providers at a recent conference, a private-practice doctor in Indiana. She had about 20 patients who lost their eligibility because of a change in the Medicaid program, and she was a sole practitioner and did not have the time or the personnel to do the paperwork to get each of her clients on the drugs they need since she was getting

out of AIDS care. It sounds like a good job for Ryan White CARE Act-funded case managers; but what do I know?

Continuing access to life-saving medications for people with AIDS remains an elusive goal. Without more clarity, uniformity, better pricing, and an increased level of purchasing power, I am not sure how we get there. ■

Christine Lubinski is Executive Director of the HIV Medicine Association.



7th International Conference on Healthcare Resource Allocation for HIV/AIDS

HIV/AIDS and the United Nations Millennium Development Goals: Are We on Target?

November 3 - 4, 2004 - Washington, DC

Call for Abstracts

At the UN Millennium Summit in September 2000, world leaders placed sustainable development at the heart of the global agenda by adopting eight Millennium Development Goals (MDGs) that set clear targets for reducing poverty, hunger, disease, illiteracy, conflict, environmental degradation, and discrimination against women by 2015.

Goal 6 commits nations to specifically “combat HIV/AIDS, malaria, and other diseases.” The UN Millennium Project—spearheaded by Jeffrey Sachs (Columbia University)—has identified 10 priority areas through which to achieve Goal 6. Four years after the UN Millennium Summit, the 7th International Conference on Healthcare Resource Allocation for HIV/AIDS (7th ICHRA) aims to assess global responses to Goal 6 as well as our relative success in addressing the related 10 priority areas.

The International Association of Physicians in AIDS Care (IAPAC) thus welcomes abstract submissions for the 7th ICHRA along the following 10 tracks (representing the 10 priority areas):

- Track 1 Access to Treatment
- Track 2 Health System Investment to Support HIV/AIDS Services
- Track 3 Prevention of HIV Transmission
- Track 4 HIV/AIDS and Vulnerable Populations
- Track 5 Integration of HIV Prevention, Care, and Treatment Efforts
- Track 6 Empowerment of Women to Combat HIV/AIDS
- Track 7 Strategies to Address HIV/AIDS in Orphans and Vulnerable Populations
- Track 8 Enhancing the United Nations Response
- Track 9 Expanding and Improving Implementation of Domestic and International Funding for HIV/AIDS
- Track 10 Empowerment of Governments and Measures for Accountability

The deadline for electronic abstract submission is August 4, 2004.

Visit www.iapac.org to submit your abstract(s).

Examining the pharmacoeconomics of HIV treatment



Patrick G. Clay

I am quite honored to come and deliver a quick presentation for you on the pharmacoeconomics of HIV treatment. First, a little bit about my background: In addition to teaching at the University of Missouri-Kansas City, I practice at the Kansas City Free Health Clinic, which is a completely free-of-charge clinic with lab and medical services. Everything is provided free-of-charge to anyone who walks in the door. We require neither proof of insurance nor of any financial source.

The guidelines for the administration of antiretroviral drugs in adults and adolescents were recently updated March 24, 2004.

Many of you are familiar with the US Department of Health and Human Services' "Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents" (DHHS Guidelines), but I took no chances in the event that some of you were not familiar. Because I do teach most of the time, I have two reasons to use these guidelines: 1) to define our goals of therapy; and 2) to illustrate the tools we use to achieve the goals of therapy.

I am going to address several issues through economic analysis. First, how to obtain maximal and durable suppression of viral load, below the limit of detection, whatever that definition may be at the time; also, how to restore and preserve the immune function. We may not be able to fully restore or bring patients back to

where they once were, but we can prevent further decline of their immune function. I will discuss improving or at least not completely losing quality of life. Finally, I will analyze the incredible reduction in morbidity and mortality that has been shown with these antiretroviral agents.

In order to get there, we need to maximize adherence to an antiretroviral regimen. I will discuss the different components and the thought processes that go into constructing one of these regimens. I am going to try to give you some insight into that based upon something that happened about 24 hours ago. Preserving future treatment options may be an answer to the question that was raised earlier: "Is an economic perspective going to be used in developing treatment guidelines in the future?" I think that as I go through my

Slide 1.

AIDSinfo
Approved Medications to Treat HIV Infection

Anti-HIV (also called antiretroviral) medications are used to control the reproduction of the virus and to slow the progression of HIV-related disease. Highly Active Antiretroviral Therapy (HAART) is the recommended treatment for HIV infection. HAART combines three or more anti-HIV medications as a daily regimen. Anti-HIV medications do not cure HIV infection and individuals taking these medications can still transmit HIV to others.

Anti-HIV medications approved by the U.S. Food and Drug Administration (FDA) fall into four classes:

Class	Generic Name	Brand and Other Names	Manufacturer	FDA Approval Date
1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)				
2. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)				
3. Protease Inhibitors (PIs)				
4. Fusion Inhibitors				

NNRTI-Based Regimens		# of pills per day
Preferred Regimen:	efavirenz + lamivudine + zidovudine or stavudine (if or stavudine) —except for pregnant women or women with pregnancy potential**	3, 1

PI-Based Regimens		# of pills per day
Preferred Regimen:	lopinavir/ritonavir (as formulated as Kaletra®) + lamivudine + (zidovudine or stavudine)*	3, 2
Alternative Regimen:	atazanavir + lamivudine or zidovudine + (zidovudine or stavudine)*	4, 1
Alternative Regimen:	darunavir + lamivudine or zidovudine + (zidovudine or stavudine)*	3, 1
Alternative Regimen:	tipranavir + lamivudine + (zidovudine or stavudine)*	3, 1
Alternative Regimen:	indinavir/ritonavir + lamivudine or zidovudine + (zidovudine or stavudine)*	3, 1

Slide 2.

Risk for Development of AIDS

CD4 < 200 cells/mm ³ Plasma Viral Load (copies/mL)		Percentage of AIDS-defining illness							
		bONA		RT-PCR		n	3 years	6 years	9 years
<	500	<	1,500	0	§	—	—	—	—
501	3,000	1,501	7,000	3	§	—	—	—	—
3,001	10,000	7,001	20,000	7		14.3	28.6	64.3	
10,001	30,000	20,001	55,000	20		50.0	75.0	90.0	
>	30,000	>	55,000	70		85.5	97.9	100.0	

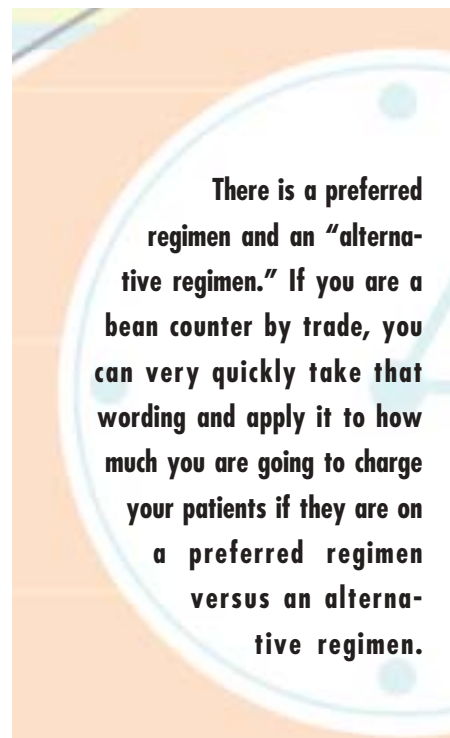
Without question, yes – time to start

presentation you are going to find the answer to that question is absolutely “yes, it will be.” One thing I am also going to touch on at the very end of my presentation is the use of drug resistance testing in clinical practice.

Slide 1 shows the four classes of currently available antiretroviral agents. This is fantastic. Ten years ago that was not the case; two years ago that was not the case. We now have the nonnucleoside reverse transcriptase inhibitors (NNRTIs), the protease inhibitors (PIs), the nucleoside reverse transcriptase inhibitors (NRTIs), and just coming on board are the fusion inhibitors. Below this, as you will see, are two excerpts from Table 12A of the DHHS Guidelines, which recommend the “preferred regimens” to start in persons who are HIV infected and meet criteria to start therapy. If you pay close attention to some of the previous presenter’s slides, she talked about pricing based upon preferred and non-preferred agents. If you look closely at the DHHS Guidelines, you find exactly the same wording. There is a preferred regimen and an “alternative regimen.” If you are a bean counter by trade, you can very quickly take that wording and apply it to how much you are going to charge your patients if they are on a preferred regimen versus an alternative regimen.

I want to point out that regimens are broken down by class of antiretroviral agent. There are NNRTI- and PI-based regimens, each regimen consisting of at least three agents. What does this mean

for pill burden for the purposes of costing? There are now co-formulations available as one drug—such as Kaletra®, which is the co-formulation of lopinavir (LPV) and ritonavir (RTV). Taking into account a preferred PI-based regimen—LPV/RTV + lamivudine (3TC) + stavudine (d4T)—



we are talking about three total drugs in an actual combination. If we look at an alternative PI-based regimen, for example, indinavir (IDV)/RTV + 3TC + d4T, we are talking about four total drugs in an actual combination—because none of

these antiretroviral agents is co-formulated. A previous presenter mentioned that caps are being imposed on the number of prescription medicines that can be filled per month. We need to have at least three drugs on board to construct an effective regimen. So, if you are limiting prescriptions, and you are counting co-formulated drugs as one prescription, the co-formulated drug would automatically move higher up on the preferred list.

I saw a fellow by the name of Bill yesterday. He was diagnosed in October 2003. His CD4 count was 368 cells/mm³. His initial viral load was 113,000 copies/ml. We did not start Bill on therapy initially, and the student who was with me yesterday was very puzzled... She said, “You have a person here who obviously needs to be on therapy. Why haven’t you started him on therapy before now?” What I asked her was to go back and look at the other medications that he is on. There was this thing about Bill’s acute schizophrenia that we had to get resolved before we could start him on medicine. While it is fantastic to put patients on antiretrovirals and get their viral load undetectable and their CD4 count up, if they are schizophrenic or psychotic, we do not really want to have them out there. So we prioritize what we are going to treat first. Bill, however, was at great risk for the development of AIDS. His viral load was 113,000 copies/ml at baseline. When he showed up yesterday, by the way, his viral load was 450,000 copies/ml and his CD4 count had dropped to

Slide 3.

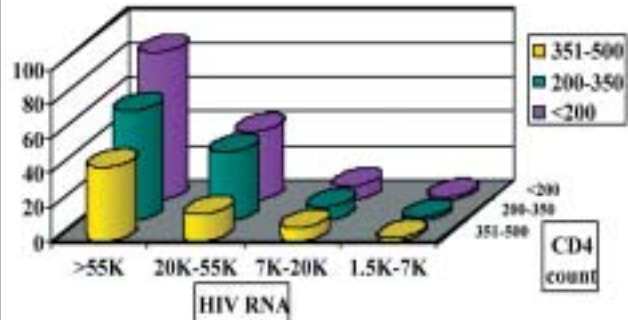
Risk for Development of AIDS

CD4 201 . 350 cells/mm ³ Plasma Viral Load (copies/mL).				Percentage of AIDS-defining illness .			
bDNA		RT-PCR		n	3 yr	6 yr	9 yr
<	500	<	1,500	3 ‡	--	--	--
501	3,000	1,501	7,000	27	0	20.0	32.2
3,001	10,000	7,001	20,000	44	6.9	44.4	66.2
10,001	30,000	20,001	55,000	53	36.4	72.2	84.5
>	30,000	>	55,000	104	64.4	89.3	92.9

Generally recommended, but controversy exists

Slide 4.

3 Year Chance to Develop AIDS



178 cells/mm³, but he was stable on his anti-psychotic meds so we were very happy about that.

Slide 2 shows the proportion of individuals who have a CD4 count of less than 200 cells/mm³ and viral loads in different ranges who are going to go on to develop an AIDS-defining illness or die due to an AIDS-related illness over the course of three, six, and nine years. We use this table to decide who should start therapy at any given time. In this particular instance, without question, it would be time to start therapy, but although our patient met these criteria, we decided not begin therapy because patients are individual

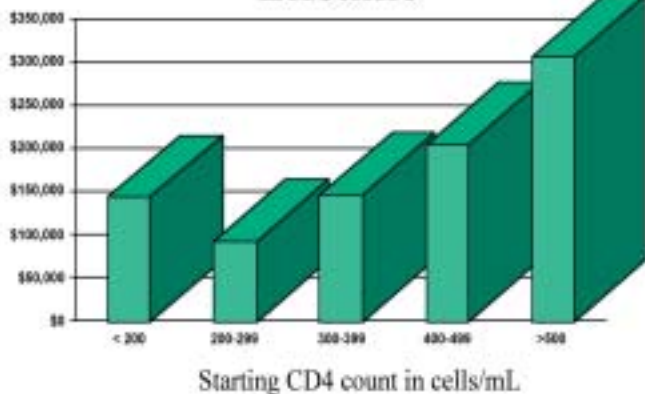
human beings. I have a number of colleagues in pharmaceutical sciences and pharmacology, and I give them a difficult time whenever they tell me they do not understand why, when I show up in the lab, my experiment is not ready to go. I tell them, "Well I do not deal with rats and I do not keep them in cages in the lab, so if I show up it does not necessarily mean they are going to show up that day." It is one of the things I try and emphasize to my students, as well as audiences, that these are humans with whom we are dealing.

There are guidelines and there are variances within the guidelines. In Slide 3, we can see where Bill falls in terms of

risk for developing an AIDS-defining illness in three, six, or nine years. Slide 4 is a graphical representation of these data. This figure is modified from the graph in the back of the DHHS Guidelines, and it shows the four strata based on HIV RNA viral load: greater than 55,000; 20,000 to 55,000; 7,000 to 20,000; and 1,500 to 7,000 copies/ml. CD4 count range is also shown. As you can tell, as the CD4 count continues to decline, the likelihood for developing AIDS within three years significantly increases, and this has a major influence on what we decide to do and how aggressive we are in doing so. A side note, when we saw Bill yesterday, he was

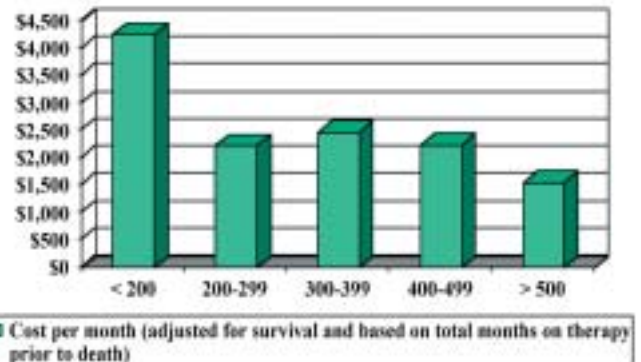
Slide 5.

Cost to Treat: Lifetime



Slide 6.

Cost to Treat: Per Month Lived



Slide 7.

TABLE 3. COSTS, CLINICAL BENEFITS, AND COST EFFECTIVENESS OF THREE-DRUG ANTIRETROVIRAL THERAPY ACCORDING TO THE INITIAL CD4 CELL COUNT.*

Initial CD4 Cell Count	Total Lifetime Costs	Life Expectancy		Incremental Cost per Year of Life Gained†	
		UN-ADJUSTED	ADJUSTED FOR QUALITY OF LIFE	UN-ADJUSTED	ADJUSTED FOR QUALITY OF LIFE
	\$	yr	yr	\$	\$
50/mm ³					
No antiretroviral therapy	41,850	1.39	1.05	—	—
Three-drug regimen	74,050	2.84	2.28	22,000	26,000
200/mm ³					
No antiretroviral therapy	55,480	3.33	2.70	—	—
Three-drug regimen	88,250	5.32	4.60	16,000	17,000
500/mm ³					
No antiretroviral therapy	70,100	7.05	6.25	—	—
Three-drug regimen	96,790	9.12	8.21	13,000	14,000

*In all analyses, the HIV RNA level was 3001 to 10,000 copies per milliliter, and the three-drug regimen was zidovudine, lamivudine, and didanosine. Data on efficacy were derived from the AIDS Clinical Trials Group 220 Study.¹

J Gen Intern Med. 2004;19:111-118. © 2004 by American Medical Association.

Slide 8.

Cost benefit of PI based triple therapy

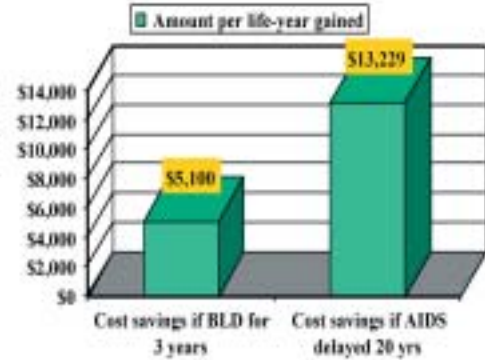


Table 3 and Table 4. Reproduced with permission of the AIDS Clinical Trials Group. © 2004 by American Medical Association. 1001-5002/04/19-111-118.

there for two and a half hours to get started on his antiretrovirals. Not only did he see me, he also saw the physician, and then went on to see his case manager, his substance abuse case manager, and his peer counselor. If Bill had a job he probably got fired because of how long he was at his doctor’s appointment yesterday.

When we start someone on therapy, one of the things that health maintenance organizations (HMOs) and other health-care payers look at is lifetime cost to treat these individuals. Along the X-axis in Slide 5 are CD4 counts. If we look at this as a one-dimensional approach only, the greater a person’s CD4 count at initiation of therapy, the higher the overall lifetime cost to treat, using just antiretrovirals, without any other factors. Costs of starting therapy at CD4 counts greater than 500 cells/mm³ are significantly higher compared to waiting until the count drops to 400, 300, and 200-299 cells/mm³. Costs for starting therapy at less than 200 cells/mm³ are elevated mostly because patients are more likely to be hospitalized. If we take this figure alone and you want to decide to develop guidelines of when you are going to start someone on therapy, then it looks like 200 to 299 cells/mm³ is the optimal time to start therapy. However, the perspective I prefer is that once we start therapy, what is the cost to treat per month lived?

In this instance what we find is that the graph gets reversed (Slide 6). Those patients

who were started on therapy with CD4 counts of greater than 500 cells/mm³ over the course of their treatment lifetime were cheaper to treat per month. If we take a cost per month approach to treating these individuals, we can see that it is better to treat them earlier on, expanding more access to antiretroviral agents.

When we adjust for quality of life, we can see the incremental cost per year of life gained is less as we treat these individuals earlier on. As we get them stabilized, we decrease viral load, we improve CD4 counts, and we improve immune function. The earlier we are able to do this, the more of a benefit we are able to give our patients.

So if they present initially with CD4 counts under 200 cells/mm³, since we see the cost to treat per month lived is considerably higher than any of the others, should we just go ahead and not offer them therapy? Most of us would

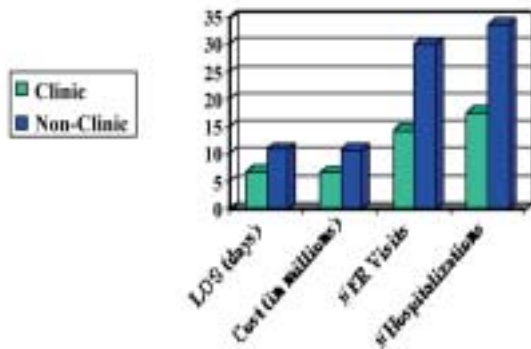
absolutely not agree to this. Even if their CD4 count was less than 50 cells/mm³, if they already had an AIDS-defining illness, we know that individuals on antiretroviral therapy cost the system substantially less than those individuals who had not been started on therapy.

Similar data were broken down and published in the *New England Journal of Medicine* about three years ago (Slide 7). They looked at the initial CD4 count of the presenting individuals, the lifetime cost to treat these individuals, the life expectancy, and the incremental cost per life-year gained, broken down by CD4 counts of 50, 200, and 500 cells/mm³. They also looked at those individuals who were on no antiretroviral therapy versus a three-drug regimen, not specifying the regimens. Total lifetime costs, were higher for those individuals with higher CD4 counts, again, reinforcing the data that I previously showed you, and as CD4 counts decrease, the lifetime costs also decrease. Overall, lifetime costs are greater for people who are on medications if you look at the cost alone.

But when we adjust for quality of life, we can see the incremental cost per year of life gained is less as we treat these individuals earlier on. As we get them stabilized, we decrease viral load, we improve CD4 counts, and we improve immune function. The earlier we are able to do this, the more of a benefit we are able to give our patients. That was a generic three-drug regimen approach, but much of the data that I use are based on

Slide 13.

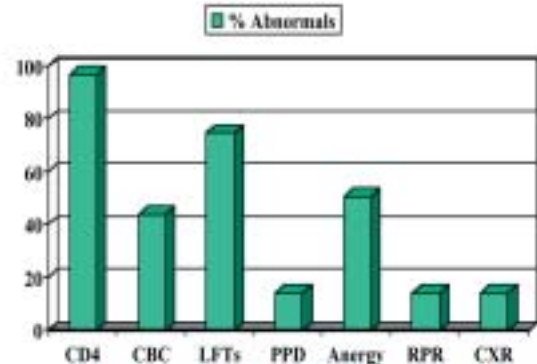
Rationale for Intensive Follow-up and Maintaining Patient Contact



Hoag MC, et al. Cost effectiveness of intensive management of HIV over long-term follow-up. JAMA. 2004;291:1041-1048.

Slide 14.

Rationale for poking, prodding and inducing anemia when diagnosing HIV infections



T. Hoag, et al. Induced anemia: a diagnostic tool for HIV infection. JAMA. 2004;291:1041-1048.

not only impact a person's life, but can also impact the savings to the institution no matter what stage of the disease treatment is started.

If you look at the change in per patient per month costs as we increase use of PIs, we will see outpatient oral medication costs go up, but that is more than offset by a decrease in hospital costs, professional costs, lab costs, and home healthcare costs (Slide 11). For every 10 percent increase in PI use, there is an average increase of about US\$135 when starting individuals on these therapies.

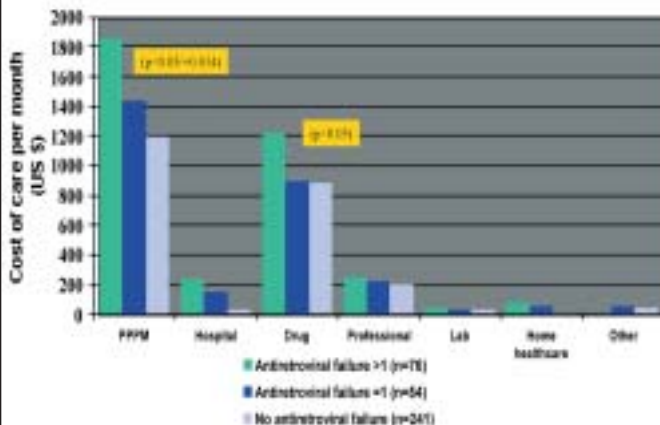
I have been discussing PIs and NNRTIs, and I have tried to stress that it

really does not make a cost difference— Slide 12 illustrates my case. A PI-based regimen—IDV + AZT + 3TC—was compared with an NNRTI-based regimen—efavirenz (EFV) + AZT + 3TC. What researchers found was that the average cost between the two regimens was not significantly different for either experienced or naive patients. Despite differences in viral load, CD4 count, and adverse events, whether a person was diagnosed with HIV or AIDS, researchers really were not able to tease out a difference between these two regimens. Both regimens were shown to be very cost effective.

It is not just getting people started on therapy that we must strive for to reduce costs to our system, it is getting them and keeping them engaged in primary care. As I mentioned earlier, Bill was meeting with a number of individuals for two and a half hours yesterday. The reason is that if we are able to start and keep patients engaged in care in our clinic, we are much more likely to achieve success. Some in-house analyses that we have done have shown that patients are more likely to get to an undetectable status if they are able to come back for at least two follow-up appointments after starting their antiretroviral therapy. That does not sound like a

Slide 15.

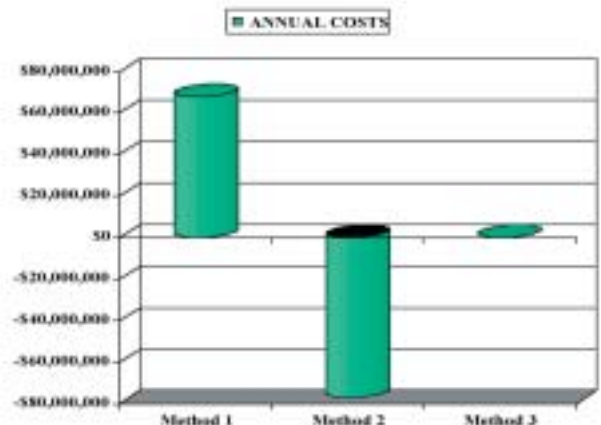
Comparative cost of primary care



Hoag MC, et al. The impact of primary care on HIV treatment costs. JAMA. 2004;291:1041-1048.

Slide 16.

Economic Impact of GART: US



Hoag MC, et al. Budget impact of the introduction of generic antiretroviral medicines (GART) in the US. JAMA. 2004;291:1041-1048.

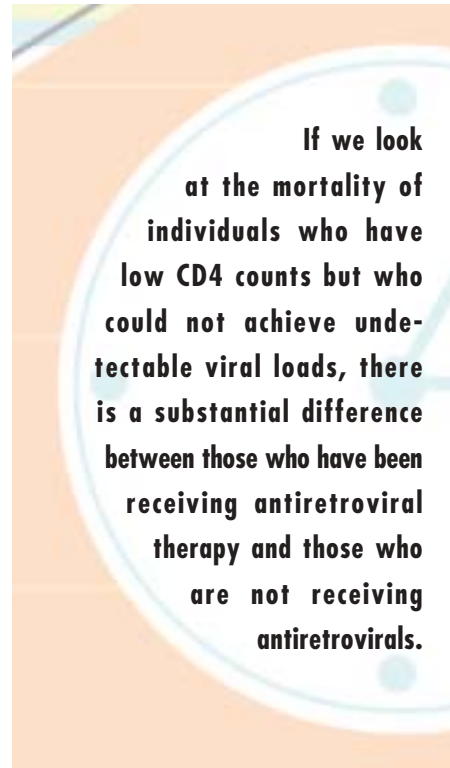
I say that tongue-in-cheek because it is not the patient who fails the drugs, it is the regimen that does not work.

What we see is that as individuals fail therapy, the cost for providing primary care continues to increase (Slide 15). So do we decide that, since they are failing therapy, and these are the patients who are costing us the most money, we will not provide antiretrovirals to these individuals? We do not make that decision, because, again, it is more than a one-step approach. It is more than a unilateral approach to looking at the cost. If we look at the mortality of individuals who have low CD4 counts but who could not achieve undetectable viral loads, there is a substantial difference between those who have been receiving antiretroviral therapy and those who are not receiving antiretrovirals. If you look at the incidence of opportunistic infections in these different groups, keeping patients on a “failing regimen” was proven to provide a substantial improvement in those individuals from a cost standpoint. The cost of one admission, actually the cost for an emergency room evaluation to treat pneumocystic pneumonia, will pay for an antiretroviral regimen for an entire year for one individual. It has been shown numerous times that preventing these opportunistic infections is paramount in overall cost savings.

I did say I would talk briefly about resistance testing. Slide 16 offers an analysis by Kit Simpson [Medical University of South Carolina] of the cost of resistance testing using three different models to determine whether resistance tests would ultimately prove cost-effective. The reason I cite this work, even though this group has gone on to show different results based upon different trials, is that depending on which methodology was used, they came up with either a benefit, a cost, or break-even. Unlike many of the colleagues with whom I converse on a routine basis, I am not a great believer in resistance testing, and it probably has to do with the limited amount of resources we have at our disposal. I guess I am just jealous of those sites that actually are able to do resistance tests, since I just have to do without them.

There was a question earlier about the actual cost for antiretrovirals, and I do not necessarily believe in using the red book, which most people use as the

standard in determining the annual average wholesale price of a medication in the United States. This is because I found it to be much more competitive if you do like the rest of the world and you get on E-bay and you ask: “How much does this cost?” So these are E-bay costs. This is how I can get my medications through E-bay. I do not know if it is legal or not. I have not actually tried to buy them... because I am sure I would be in trouble in three different states.



Slide 17 shows the annual cost for the PIs. For those of you who are engaged in doing this on a routine basis, if we had those 60 individuals who were able to take ritonavir (RTV) in the original RTV trial, and they were on 600 mg of RTV twice a day, the cost for their PI alone would be about US\$46,000 a year. Now most of us have used RTV to boost, or pharmacokinetically enhance, other agents to improve the activity of the other agents. We can see that the cost is still substantially higher, and this is not even using the drug at its full dose. This is 200 mg a day. Again, as was mentioned earlier, in some states there is a cap on the number of drugs, so you can see why a state such as Texas would want to cap RTV at 200 mg a day because the cost of

RTV 200 mg a day is over US\$30,000 a year.

Slide 18 shows the cost for one NRTI. For example, the price of emtricitabine (FTC), a recently approved once-a-day drug, is running just over US\$3,000. Combivir® is prorated as though it were two agents, so Combivir® is actually twice this price because it is actually two drugs in one. So we can see that the average price for one NRTI is a little over US\$4,000 per year.

Slide 19 shows two NNRTIs—EFV and nevirapine (NVP). Efavirenz costs a little over US\$5,051 a year and NVP costs about US\$500 less per month; you multiply that times 40 million individuals who may be on antiretroviral therapy and that is a substantial cost savings.

Slide 20 shows the annual cost for an antiretroviral regimen, this is just the antiretroviral. It is not the labs. It is not providing case management, substance abuse case management, or any of the other ancillary services that I talked about. It is not hospitalizations. This is roughly about US\$20,000 to US\$25,000, and takes into consideration the average price of a PI, the two NRTIs, and an NNRTI. The reason I added all of those up is because that is actually the regimen that we started Bill on yesterday—all four of those agents from all three classes of available antiretrovirals. We have the temporary benefit in Missouri of covering all approved antiretrovirals. I believe the number of drugs available through Missouri’s AIDS Drug Assistance Program (ADAP) is second only to New York State. Because of that, we were able to stabilize Bill on his anti-psychotic medicines through ADAP, and we now have him on antiretroviral therapy.

What I have tried to present today is some brief background—some of which is published, much of which has been presented elsewhere. Finally, I think Abbott Laboratories has brought to the forefront with their RTV pricing increase last year exactly what is going to be coming along in a few short months to years with antiretrovirals. ■

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Untangling the economics of drug pricing



Joshua P. Cohen

I am honored to be here, but I need to issue a disclaimer: I am a health economist, but my main focus is on reimbursement issues—that is, pharmacy benefits management. I have also done some work on prescription to over-the-counter switches but I have not done much work on AIDS drugs, at least not in specific detail, nor am I an expert on drug pricing, *per se*. However, that being said, reimbursement and drug pricing are certainly related, as we will see shortly.

The theme throughout my talk will be that patient access to prescription drugs is a function of three items, the first being “availability” of the drug. That is, it needs

to be approved or go through the regulatory approval process, and implemented by the US Food and Drug Administration (FDA), and FDA counterparts abroad. Second, and very important, is “coverage.” Christine [Lubinski] touched on that topic. In fact, she gave a detailed talk on coverage, and I will supplement some of what she said. Finally, although this is more self-explanatory than the others, the third item will be “personal income,” because some fortunate people may not even need to be covered, may not need insurance. They may simply have income sufficient to pay for their prescription drugs. Most people, of course, are not this fortunate.

I will cover the main FDA regulatory initiatives to speed up and improve the approval process, and then I will turn my

attention to coverage issues. I am going to give a brief historical overview, going back about 15 years. Finally, I will give a brief, quick, and dirty case study that I designed last week, examining the placement of AIDS drugs on several US formularies, as well as the Dutch National Formulary. Of course, many of you may wonder why I chose Holland. Well, I have spent half my life in Holland, I have advanced research there, and I have studied there, so it was a natural reference point for me.

So again, access is a function of availability, coverage, and personal income.

Availability depends on regulatory mechanisms and the research and development (R&D) environment. Before I look at availability and coverage separately, let me briefly touch upon a controversial

FDA's expedited development and approval programs

Program	Share by disease indication		
	Cancer	HIV/AIDS	Other
Subpart E approvals (12/88-2/99)	25%	50%	25%
Accelerated approvals (6/92-6/03)	33%	37%	30%
Priority review approvals (1/97-9/03)	20%	9%	71%
Fast track approvals (9/98-6/03)	39%	21%	39%

Source: Tufts Center for the Study of Drug Development

topic, the relationship between the R&D environment and pricing. Suffice it to say, without a functional and profitable R&D environment, drugs would not be developed and made available to the general public in a timely and efficient manner. The R&D environment depends to a degree on pricing. Some say, controversially, that a free market for pharmaceuticals, with no price controls, is essential for long-term growth and innovation; others contend that this is not the case. As we will see, a completely free market for pharmaceuticals does not exist even in this country.

Let me briefly state my take on the pricing debate. We need to recognize the importance of patent protection and a pharmaceutical company's ability to market a drug at a price that matches supply and demand. This being said, I think we must all acknowledge that when making decisions pertaining to drug pricing, we enter the realm of ethics and the need to balance economics with our moral duty to people in need, especially when we are dealing with life-saving treatments, such as AIDS drugs. Needless to say, drug discovery and development take time, money, and they are labor intensive. Basic research can take decades, discovery can be like finding a needle in a haystack, and development requires numerous, lengthy clinical trials. Only one in five investigational drugs actually makes it to the pharmacy shelves.

Availability, of course, depends on many things, not least of which is R&D for new drug development. It also depends

on the FDA approval process, and issues related to the marketing of drugs, such as patents. Let me give you a brief historical overview of regulatory initiatives that were intended to improve this process, starting with the Hatch-Waxman Act of 1984. Hatch-Waxman attempted to balance competing objectives—innovation, price competition and prescription drug affordability. Not an easy balancing act. Hatch-Waxman sought to shorten the time it takes for generics to reach the market by creating the Abbreviated New Drug Application (ANDA) process, which eliminated lengthy and expensive clinical trials for generic products.

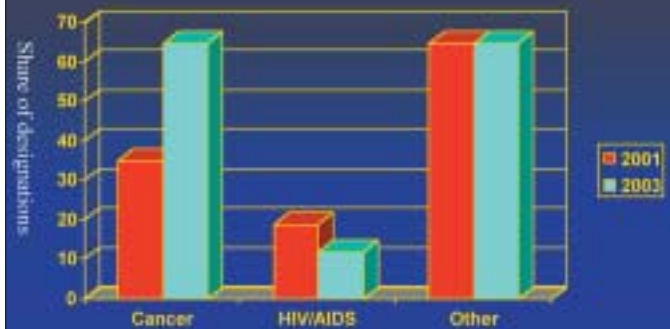
Since Hatch-Waxman, there has been continued public concern about the length of time for FDA review, limited access to drugs during clinical trial testing, and the lack of existing therapies for certain disease states, including HIV and AIDS. As a result, there have been more regulatory initiatives, including the expedited approval programs starting in 1987; the Prescription Drug User Fee Act (PDUFA) in 1992, which charged pharmaceutical companies user fees for review of New Drug Applications (NDAs); and the Food and Drug Administration Modernization Act (FDAMA) of 1997, which formally introduced the Fast Track Initiative.

From 1987 through 1992, the FDA developed and implemented several programs designed to expedite patients' access to emerging therapies, either by allowing patients access to unapproved therapies, or by accelerating the drug

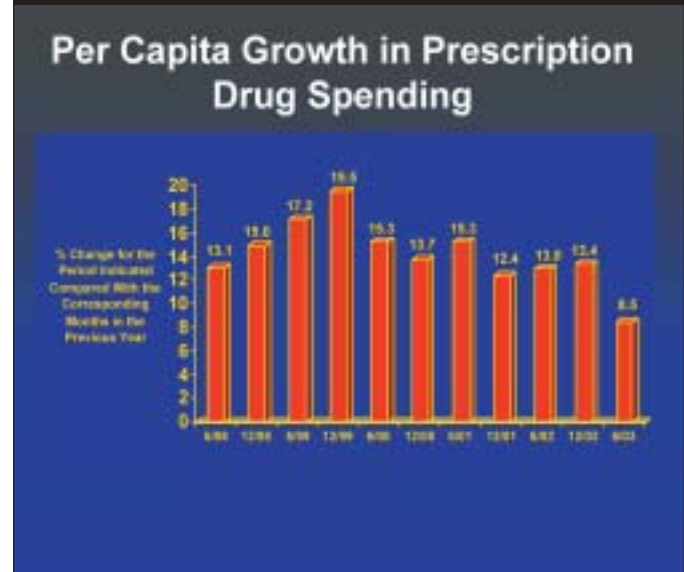
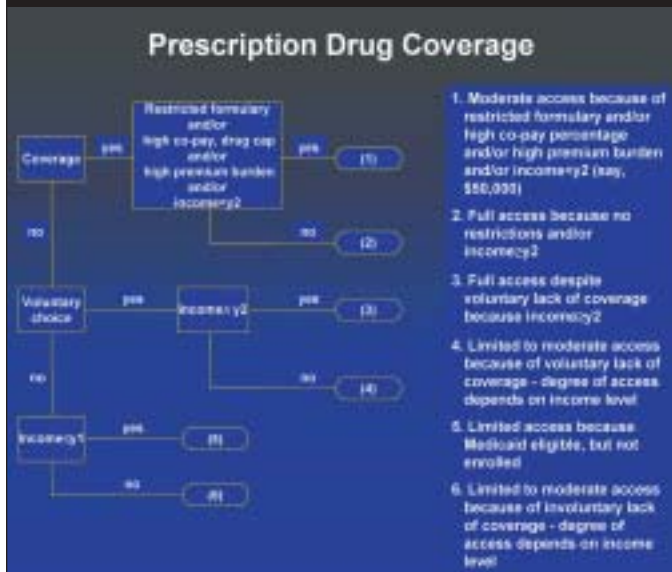
development and approval process. With Treatment Investigational New Drugs (treatment INDs), desperately ill patients gain access to a drug while the clinical development and FDA review continue. For treatment INDs, drug sponsors may not commercialize an investigational drug by charging a price higher than that necessary to recover costs of manufacture, research, and development. Thirty-nine of these have been granted, among which eleven were for AIDS drugs. Then there are the New Drug Submissions (NDSs) approved under the Center for Drug Evaluation and Research (CDER) Accelerated Approval Programs, Sub-Part H. Thirteen out of 38 of drugs approved through CDER have been AIDS drugs.

The FDA fast-tracked azidothymidine (AZT) in 1987. This first of now 19 AIDS drugs passed through the FDA approval process in four months. Another example is the fast-track approval of saquinavir (SQV), which was approved just three months after the filing of its NDA; and, in 1996, indinavir (IDV) was approved in a little over one month. In all, the FDA's expedited development and approval programs have particularly focused their attention on AIDS drugs, as well as cancer drugs (Slide 1). That is the good part. However, the share of AIDS fast-track designations, for a variety of reasons, have fallen to less than 20 percent in 2001 and less than 10 percent in 2003 (Slide 2). If we summarize the ups and downs of AIDS drug R&D, many drugs have been approved. There is no question

Fast track designation by type of disease



Source: Tufts Center for the Study of Drug Development



about that. And many of these drugs are clearly life-saving drugs, and are very important to the patients and their care providers. There has been improved efficacy, improved compliance, and improved dosing, but it certainly has not met the growing worldwide need. We need to focus our attention not just on the United States, but worldwide, where millions need the medications and do not have access to them.

Now, we will move to the second access factor: coverage. Let's talk about coverage. In this country, and I stress, in this country, a person's degree of drug coverage depends on insurance status, and insurance status is co-determined by socioeconomic status, factors such as income, employer, age, where one lives; and last (and unfortunately unique to the United States) but certainly not least, preexisting conditions. This is certainly a unique American phenomenon.

In Slide 3, for the sake of convenience, I make the ideal assumption that the needed drugs are "available." If all the drugs are out there, the flowchart on this slide shows the relationship between degrees of access and coverage. We can define access in terms of coverage and earned income. The first question is: "Does a person have coverage?" If the person has coverage, we have to look at restrictions in the formulary, possible co-pays, and a high premium burden as ways of unfortunately limiting their degree of access to drugs that are available. Having coverage is not the whole story. This is fairly obvious to most of us, but what I have done here is

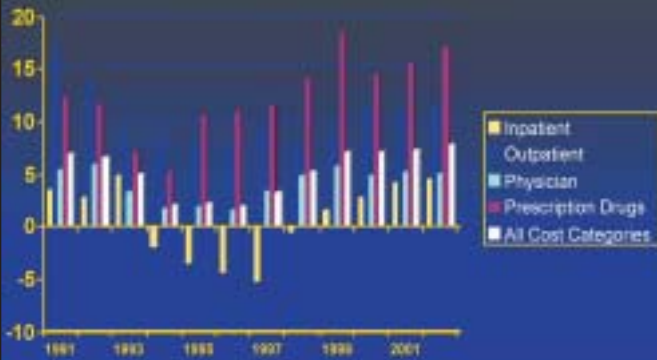
try to summarize the main points of the relationship between coverage and access. Now if you do not have coverage, it is not necessarily a bad thing if you are really well off. Of course US\$50,000 may not sound like a lot to some in the United States, but suppose it is US\$100,000 or US\$200,000 or at whatever level we establish the cut-off. For those of us who are well off, perhaps coverage is not an important issue, but for most of us coverage is important and insurance status is important.

Then there is the fact that in this country, coverage is a voluntary choice on the part of the patient, the enrollee and his or her employer, for instance. Again, while this may be the case in the United States it is not the same in some other countries. Coverage in the United States is completely voluntary. There is no mandatory mechanism mandating employers to provide coverage. Many do, many do not. The same thing applies to the individual patient. There is no one saying that you have to have coverage, such as the case in Europe, where it is a mandatory mechanism, providing a way of spreading and pooling risks across the population. In the United States we do not have that mechanism, even for those in Medicaid or who are Medicaid-eligible. The earlier talk included the fact that many HIV-positive patients, up to 50 percent, are indeed in Medicaid, but up to 50 percent who are Medicaid-eligible may not even be enrolled in the program at any given time. So many of those people also do not have coverage, despite the fact that

Medicaid, compared to private plans, is a fairly generous program across the 50 US states. Of course there are differences, there are nominal co-pays, for example, but many of those who are Medicaid-eligible are not enrolled in the program.

Now contrary to conventional wisdom—and here is where I deviate slightly from the previous talk—coverage of pharmaceuticals has actually increased dramatically throughout the 1990s, and ironically, I think that is what has been part of the problem of perception. We see that we have perhaps reached a turning point in 2000, where our own out-of-pocket costs are now going up again. But, certainly throughout the 1990s, as part of the "managed care" revolution, and I know we have been prone to bash managed care, but as part of the managed care revolution, prescription drug coverage actually increased dramatically. Now it has become an expensive proposition. Providing prescription drug coverage became something of a burden to the managed care companies, to government and to Medicaid. Why? Because spending was increasing at rates of up to 19.5 percent back in 1999. It has come a bit more down to earth recently. As shown in Slide 4, the most recent Milliman USA Health Cost Index Survey estimate was that it increased 8.5 percent last year at this time. I do not know if that is a one-off blip, but clearly prescription drug spending has been increasing at a much higher rate than the other components in healthcare (Slide 5): inpatient, outpatient, and physician services.

Annual % Change in Spending per Cost Category



Source: Milliman USA Health Cost Index Survey (2002)

While our out-of-pocket costs have gone down—and I am not speaking now to HIV-positive patients, but speaking generally—prescription drug spending overall has increased. This makes sense, because if you provide coverage, as the Rand experiment 20 or 30 years ago proved, and basically subsidize pharmaceutical care, there will be more utilization, thus more spending. I think what all of us fail to see, though occasionally we do see well thought-out pieces in the *New York Times* or *Wall Street Journal* which point out the fact that prescription drugs are still only 9 or 10 percent of the overall healthcare spending pie, is that maybe there is some short-sightedness on the part of certain insurers and Medicaid and the government. We just heard Patrick [Clay] talk about cost-benefit and cost-effectiveness analyses; perhaps prescription drugs actually are a somewhat cost-effective component. It is a rising component, but it is not really a big part of the healthcare spending pie and it is perhaps reducing the growth rate in inpatient and outpatient, and maybe even physician services. There is no proof of this, but we can certainly see that while prescription drug spending was outstripping all the other components by a margin of 3 percent, inpatient costs were growing at 2, 3, 4, and 5 percent per year instead of 15 percent per year. Maybe there is a trade-off in growth rates.

What has been the response to the increase in drug spending? In Western

Europe, Japan, Canada, and other countries as well, where healthcare is largely government-run, insurers have responded by cutting drug budgets, raising co-pays, and a few have imposed cost-effectiveness

In the United States, most people who have insurance have private insurance, and private insurers have responded to increased drug costs by caps on drug spending and formulary restrictions. They have also, of course, introduced the multi-tiered co-pay arrangement in a big way...

thresholds prior to admitting new drugs to the formulary. Australia is the best example of a country that has introduced these thresholds. It is quite controversial, and they especially apply to breakthrough medications. In the United States, most people who have insurance have private insurance, and private insurers have

Cash Flow with Government-Sponsored Drug Insurance



responded to increased drug costs by caps on drug spending and formulary restrictions. They have also, of course, introduced the multi-tiered co-pay arrangement in a big way because five or 10 years ago, you did not have this three-tiered approach, and now I think from 60 to 70 percent of insurers have a tiered approach to co-pays.

Let me briefly explain other ways to reduce drug spending, which have included price controls. Many countries have imposed direct price controls. The United States generally does not have direct price controls other than the federal ceiling price, which is a Veterans Administration (VA) price. Still other countries have gone down a different path. It is called “reference pricing,” based on a web, a nexus of cash information and also drug flows between the government intermediaries, patients, and providers (Slide 6).

Let’s start out looking at price controls with the patient who gets his prescription and goes to the local CVS/pharmacy or Rite Aid pharmacy to get a prescription filled. The pharmacy has ordered the drug from a distributor and the distributor got it from a manufacturer. When insurers enter the game, particularly when pharmacy benefit managers (PBMs) enter the game, it gets far more complicated, with payments, rebates, and reimbursements. The pharmacy collects payments from patients (the co-pay) and health plans, and pays distributors for products. Retailers and distributors each take a percentage from what is called average wholesale price (AWP), which is a list price. It is like the price on a car. It is not

Formulary Coverage of Nucleoside Reverse Transcriptase Inhibitors

Ingredient	Kaiser Permanente	Aetna (2 tier closed)	Harvard Pilgrim (3 tier)	BCBS WA state (3 tier)	Netherlands national formulary
abacavir	\$\$\$\$\$ *	Tier 2	Tier 2	Tier 2	full coverage
didanosine	\$\$\$\$\$	Tier 2	Tier 2	Tier 2	full coverage
lamivudine	\$\$\$\$\$	Tier 2	Tier 2	Tier 2	full coverage
stavudine	\$\$\$\$\$	Tier 2	Tier 2	Tier 2	full coverage
zalcitabine	\$\$\$\$\$	Tier 2	Tier 3	Tier 2	full coverage
zidovudine	\$\$\$\$\$	Tier 2	Tier 2	Tier 2	full coverage
lamivudine+zidovudine	\$\$\$\$\$	Tier 2	Tier 2	Tier 2	full coverage
abacavir+lamivudine+zidovudine		Tier 2	Tier 2	Tier 2	full coverage
emtricitabine		Tier 2	Tier 3		Under review

* On a scale of \$ to \$\$\$\$\$

Formulary Coverage of Protease Inhibitors

Ingredient	Kaiser Permanente	Aetna (2 tier closed)	Harvard Pilgrim (3 tier)	BCBS WA state (3 tier)	Netherlands national formulary
atazanavir		Tier 2	Tier 3		NA *
amprenavir	\$\$\$\$\$	Tier 2	Tier 2	Tier 2	full coverage
indinavir sulfate	\$\$\$\$\$	Tier 2	Tier 2	Tier 2	full coverage
saprinavir	\$\$\$\$\$	Tier 2	Tier 2	Tier 3	full coverage
lopinavir/ritonavir		Tier 2	Tier 2	Tier 2	full coverage
ritonavir	\$\$\$\$\$	Tier 2	Tier 2	Tier 2	full coverage
nelfinavir	\$\$\$\$\$	Tier 2	Tier 2	Tier 2	full coverage
mesylate					
fosamprenavir			Tier 2		NA *

* NA= not approved for marketing in the Netherlands

the actual price paid. It is the sticker price.

On the insurers' end, pharmaceutical companies also provide rebates to PBMs for moving market share and credit distributors. Pharmacy benefit managers negotiate on behalf of insurers; they take their cut of rebates but do pass on a portion to the health plan. Pharmacy benefit managers can thus exert some downward pressure on drug prices; estimates are between 10 and 30 percent. Unfortunately, PBMs are relatively secretive about their rebate deals, and they do not reveal to researchers or others the exact percentages that they are getting off of AWP. We have to estimate these percentages, and when you say 10 to 30 percent, it is clearly a broad range. Again, a common feature of formulary design is the three-tiered co-pay approach through which enrollees pay lower co-pays for generics than for brand names, higher prices for brand names off the formulary than on the formulary. The pharmacy's incentive to participate in this nexus is based on its virtual guarantee of access to an enrollee base of health plans. Again, you are talking about basically 200 million people, or it may be more because almost everyone now is in managed care of some sort. Pharmacy benefit managers have between 200 and 220 million covered lives, and in exchange for this access, the pharmacies agree to a reimbursement formula established by the PBMs, which is expressed as a discount off of AWP. They do get a dispensing fee per prescription.

Clearly there is controversy and confusion surrounding the complex web of cash

information to drug flows between the pharmaceutical companies, wholesalers, government, PBMs, and end users, especially concerning drug prices. If the retail price at the pharmacy for a particular dosage and quantity of a brand-name pharmaceutical was US\$100, then on average an uninsured individual is paying the highest amount. Christine [Lubinski] in her presentation and José [M. Zuniga] in his introduction, both touched upon the fact that we have something like 40 or 45 million uninsured individuals in the United States; they are paying the highest price, the full retail price for that drug. Health maintenance organizations (HMOs) and insurance companies would pay between US\$65 and US\$80, Medicaid pays around US\$70 (though it could be between US\$60 and US\$80), and the VA pays between US\$50 and US\$60. We have a confusing array of drug prices. We have the retail price, the highest in the chain of distribution, and really none of us probably know what the retail price is, because when we go to the pharmacy, at least those of us of who are insured, we are paying a co-pay. We do not really know what the price is and for the most part, physicians and providers do not know either. That is part of the moral hazard.

The fact is, once there is coverage, since no one really knows what the price is, sometimes you can have what is called "physician-induced demand" for certain products. People will just say, "Oh look, you are covered. You can take this or that pill." It does not apply as much to AIDS drugs

because these are still life-saving treatments, but it certainly applies to other drugs that we know about from direct-to-consumer advertising. We have then the AWP, which is a list price. It is referred to as a sticker price. Most estimates are that discounts for HMOs and large purchasers are more than 20 percent off AWP. And then there is the average manufacturer's price (AMP), which is the price paid to a pharmaceutical manufacturer by wholesalers for drugs distributed to retail pharmacies. Finally, there is the only direct price control in the United States, which is the federal ceiling price, or maximum price manufacturers can charge for the Federal Supply Schedule.

Now to get back to what I briefly mentioned before, reference pricing. In an effort to contain drug spending, Germany, Australia, New Zealand, and The Netherlands allow reference pricing. Let me take the Dutch as an example. The Dutch formulary reimburses at the level of the cheapest product in a therapeutic "cluster." The government also imposes price ceilings at the same time, and these are based on the average retail price of drugs in four surrounding countries. In Holland, it is important to note that non-clusterable products, which are about 15 percent of the products, and which tend to be life-saving drugs for diseases such as HIV, are put on a separate list and are always reimbursed in full. In 2005, however, all new non-clusterable products will have to pass a cost-effectiveness threshold, a test prior to

Formulary Coverage of Non-Nucleoside Reverse Transcriptase Inhibitors

Ingredient	Kaiser Permanente	Aetna (2 tier closed)	Harvard Pilgrim (3 tier)	BCBS WA state	Netherlands national formulary
delavirdine mesylate	\$\$\$\$\$	Tier 2	Tier 2	Tier 2	NA *
efavirenz	\$\$\$\$\$	Tier 2	Tier 2	Tier 2	full coverage
nevirapine	\$\$\$\$\$	Tier 2	Tier 2	Tier 2	full coverage

* NA= not approved for marketing in the Netherlands

Formulary Coverage of other AIDS pharmaceuticals

Ingredient	Kaiser Permanente	Aetna (2 tier closed)	Harvard Pilgrim (3 tier)	BCBS WA state (3 tier)	Netherlands national formulary
tenofovir disoproxil fumarate			Tier 2	Tier 3	full coverage
enfuvirtide	\$\$\$\$\$ prior authorization		Tier 3	Tier 2	full coverage

being reimbursed in full. It will be similar to the situation that currently exists in Australia.

Reference pricing is an approach to reimbursement for pharmaceuticals you will be hearing more about in the coming months in the United States as well. Some health plans are experimenting with a version of reference pricing, and reimbursement based on functional equivalence is closely akin to reference pricing. In reference pricing schemes, products are clustered into groups, as I said, which are based on therapeutic effects. In contrast to generic referencing, therapeutic referencing treats compounds with different active ingredients as equivalent, despite possible differences in efficacy and/or side effects. They cluster on-patent with off-patent compounds. This is often considered quite controversial, even in The Netherlands. The payer—the insurer—sets a reference price for each cluster based on a relatively low-priced product in the cluster. Say you are looking at second-generation antihistamines. Suppose that Allegra® was the cheapest. That would be the product that would be given the reference price. The reference price is the maximum reimbursement for all products in the group. Suppose you are a patient in Holland and you want Claritin®. Fine, you can get Claritin®, but you pay the surcharge, whatever the difference is between the reference price and the price for Claritin®.

Now the AIDS drugs and other life-saving treatments are put on the non-clusterable list, what is called 1B in The

Netherlands, and I believe it is the same in Australia, Germany, and New Zealand as well. Though I am not sure about this, I am assuming that it is the case, so 15 percent of drugs are considered “life-saving,” and therefore they are fully reimbursed.

In Slides 7-10 you can see that Kaiser Permanente and the Blue Cross/Blue Shield plans, for instance, include AIDS drugs on their formularies. The dollar signs simply refer to the tiering of that product. If it has few dollar signs, it is a low-priced product; if it has many dollar signs, it is a high-priced product. We do not know exactly how much people are paying in co-pays, but clearly Kaiser Permanente and the Blue Cross/Blue Shield plans are putting these products on their formularies. Aetna and Harvard Pilgrim coverage may have changed slightly since I created these slides, but I believe that coverage is for the most part the same. Kaiser Permanente has numerous formularies, not just one. We picked a representative formulary. Some of the products are not on certain formularies; other products are on all formularies.

If we compare it to The Netherlands' national formulary, we can see that these drugs have been put on a non-clusterable list and they have been given full coverage, other than the products that are labeled as “N/A,” which are not approved by the local FDA counterpart. You have to look at this very carefully. I mentioned availability as being an important component

of access. Certain drugs, Baycol® is perhaps the best example, never made it through the approval process in The Netherlands, in fact never made it through the approval process in several European countries. They made it in the United States and approval later had to be withdrawn. That does not mean that The Netherlands or European FDA counterparts are more or less cautious than we are, but it certainly tells us a story about globalization. We are not yet there in terms of harmony of our drug approval processes and I do not think we ever will be, because there is a culture that is different at the FDA from its FDA counterparts such as the European Agency for the Evaluation of Medicinal Products (EMA). So, certain drugs are just not available. But, the ones that are available are given full coverage.

To recap, availability depends on the regulatory initiatives that are in place to increase availability, but they do require fine-tuning to meet patient demand for newer medications. For instance with AIDS drugs, only one new, novel drug has been approved over the past few years, and certainly something needs to be done about that. Moreover, we have seen that third-party payers are increasingly restricting coverage. Thank you. ■

Joshua P. Cohen is a Senior Research Fellow at Tufts Center for the Study of Drug Development.

Defining the impact of AIDS drug pricing on the public sector



Lanny Cross

Owish to thank the International Association of Physicians in AIDS Care (IAPAC) for inviting me to join you all here today to discuss the impact of AIDS drug pricing on the public sector.

My estimate of expenditures for antiretroviral drugs in the year 2003 in New York State, by payer, is shown here (Slide 1). There is some guesswork involved in this, however. The one thing I am fairly certain of is that the ratio of Medicaid to AIDS Drug Assistance Program (ADAP) is just a little over three people on Medicaid getting antiretroviral drugs for every one person on ADAP. Based on recent corrections to some previous esti-

mates that we had, and more recent data that we picked up from the Veterans Administration (VA), we are pretty confident that these numbers are pretty close, although there are still some estimates figured in. The biggest guess is with the "Private/Other" category. We lumped a number of smaller things in there so its accuracy is least certain, although I think it is still quite close.

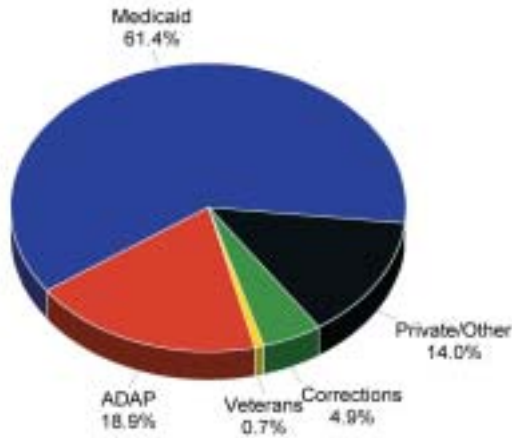
So, New York State spent somewhere over US\$800 million in 2003 on just antiretroviral drugs. This cost, spread across various programs such as Medicaid, ADAP, and the VA, is not the same mix that you are going to find in every state. Medicaid in New York is a very inclusive program that covers a high number of people in need of antiretroviral drugs. Christine [Lubinski] has said, "Medicaid

is not universal healthcare for the poor." In New York, it is. You do not have to be disabled to get it; you just have to be poor. In some states, the ratio of Medicaid to ADAP will actually reverse, because Medicaid is such a closed system and so difficult to get into that ADAP will have to pick up that much more of the burden.

Here is where we get into the detail. Just for perspective, I think that the antiretroviral drug market in the United States is about US\$4 billion per year, and ADAP and Medicaid are probably good for at least US\$250 million and US\$1 billion of that, respectively. There are a mix of government prices and purchasing systems. The purchasing system used in a distribution system to some extent dictates how you are going to get your pricing. There is the Federal Ceiling Price, there is a Federal

Slide 1.

Estimated Expenditures for HIV/AIDS Drugs in 2003 New York State - by Payer



Slide 2.

Pharmacy Network Net Cost



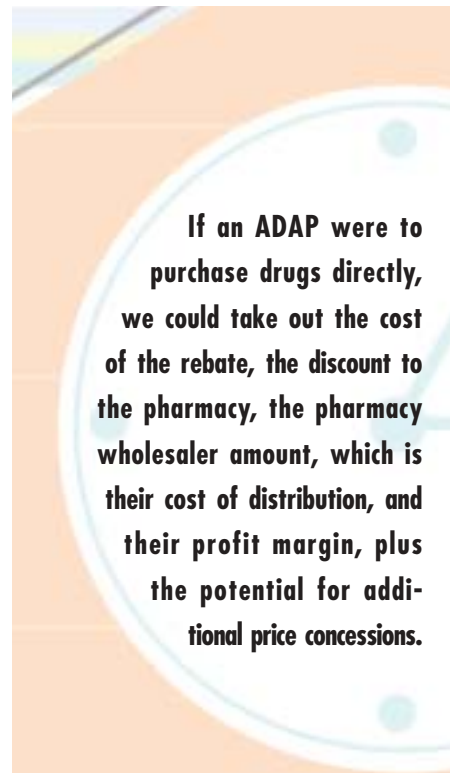
Supply Schedule, and there is a Public Health Service 340B price, for which ADAPs are eligible. All of these mean you take possession of the drugs, you get the drugs, and then you distribute them.

The other primary type of system is the pharmacy network system, where you reimburse a broad network of pharmacies at average wholesale price (AWP), typically minus some percentage, plus a dispensing fee. That is the system that Medicaid uses. Medicaid also receives rebates under Omnibus Budget Reconciliation Act (OBRA) legislation, and ADAP receives rebates under the 340B Rebate option. I will not go into the 340B Rebate option in great detail.

The way a Medicaid or ADAP rebate works is that for a brand-name drug you get a minimum of 15.1 percent off the average manufacturer's price (AMP), which is a secret price. Though you cannot know what that price is, you get 15.1 percent off the AMP, or the difference between AMP and the best price that the pharmaceutical company is giving to a private sector payer, if it is larger. Plus, you get a supplemental rebate if the AMP price increases exceed the inflation rate as stated by the Consumer Price Index (CPI). Inflation is calculated back to the initial introduction of the drug, which is a little complicated, but it means typically when you are in a low-inflation period, such as we have been, the rebates get larger if the drug prices have increased more quickly than the rate of inflation. If you get a 5 percent price increase, what an ADAP or Medicaid is really going to see

is a net cost creep of about 0.50 percent or so per quarter, and it keeps getting recalculated each quarter, keeping track with the CPI.

The rebate for generic drugs, of which there are no antiretroviral drugs in this case, is 11 percent of AMP; the 340B



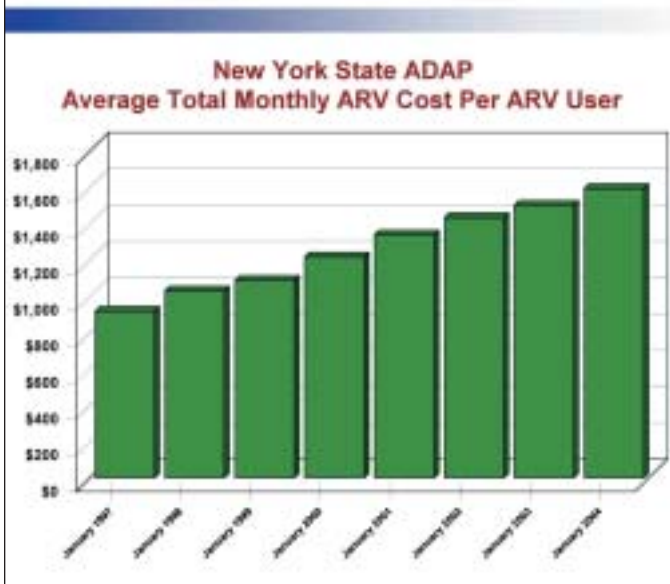
discount price is simply AMP minus that rebate amount.

Slide 2 is an attempt to make things a little simpler to comprehend. When you are direct purchasing, that price is going to be the bottom block of the figure. This

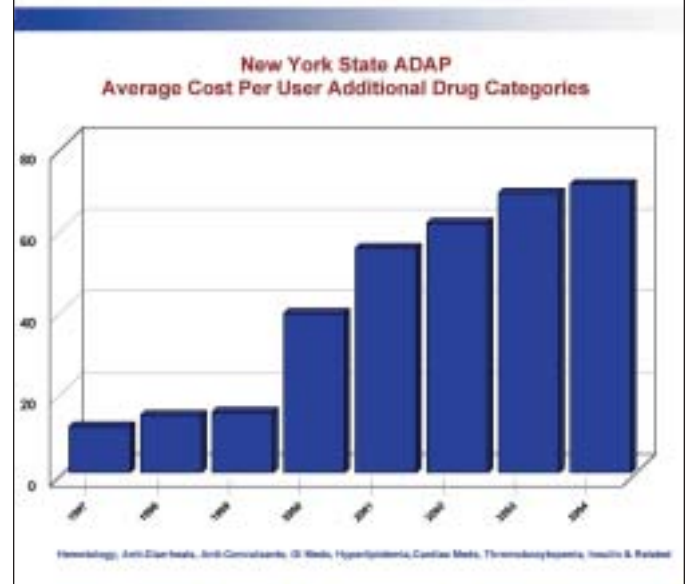
is a hypothetical drug that costs US\$100 at AWP. I say it is very hypothetical in the antiretroviral drug business because we would love to see a US\$100 drug, and there is nothing anywhere close to that. The AWP is the retail, or list, price. The figure shows a discount. The pharmacy does not get the full amount as discounted. In this case, the example was discounted 10 percent. The next amount goes to the pharmacy and the wholesaler; it is their cost of doing business, for taking possession of the drug and moving it to the pharmacy; and to the pharmacy for handing it to the individual, and all of the counseling and handling costs involved in that. The next piece comes back as a rebate. But the amount of money going to the pharmaceutical company is really US\$68 in this hypothetical situation. That is important, because we talk a lot about drug pricing but it is very convoluted, and the price that you see or that we are even able to talk about is not necessarily the price that anyone is paying. Joshua Cohen alluded to this issue in his presentation (see "Untangling the Economics of Drug Pricing," pages S23-S28).

New York State's ADAP pays AWP minus 12 percent to the pharmacy. This is the same rate that Medicaid pays. If an ADAP were to purchase drugs directly, we could take out the cost of the rebate, the discount to the pharmacy, the pharmacy wholesaler amount, which is their cost of distribution, and their profit margin, plus the potential for additional price concessions. There is a difference between this price,

Slide 3.



Slide 4.



which is closer to the net cost, and an AWP minus 12 percent price, which is what you would see in government data.

There are variations in price increases for individual drugs. You have got the slow steady creep of zidovudine (ZDV). It is the turtle in the race. The company that manufactures this drug takes regular price increases, lets inflation grow, and takes advantage of that CPI penalty or makes sure that there is always headroom so it can grow. When efavirenz (EFV) entered the market in 1998, we had a problem. It was priced substantially higher than other drugs. It set a new pricing point. The only drug that has broken from that trend is emtricitabine (FTC), for which we are seeing cost parity because it has essentially the same effectiveness as lamivudine (3TC).

Whenever we have a new drug breaking new pricing points, it has a negative impact for payers for the next round of drugs coming through the pipeline. Besides some of my other problems with ritonavir (RTV), it really affected the scale. Again, in a similar scenario, we had consistency on pricing for quite a while. Then enfuvirtide (ENF), admittedly a new class of drug, was introduced, but following that there was a new price point; and the price points are coming up further. For fosamprenavir (FPV), in fairness, a boosted dosage is about half the amount of an unboosted dosage, but we are still trying to see what the mix is going to be between boosted or unboosted dosages. The big issue is probably the substantial

difference in many cases between the actual cost and the public price. There is a substantial difference between what it looks like we pay and what we actually do pay.

Slide 3 shows the average total monthly cost of antiretroviral drugs per user, and here we have a very clear trend. It is generally a result of more drugs being used in combination. Plus, there are newer drugs coming in, and those new drugs tend to be higher priced, despite the efforts we make to keep prices down. It is also due to regular price increases on the part of most pharmaceutical companies. It is getting more expensive to keep a person on antiretroviral therapy.

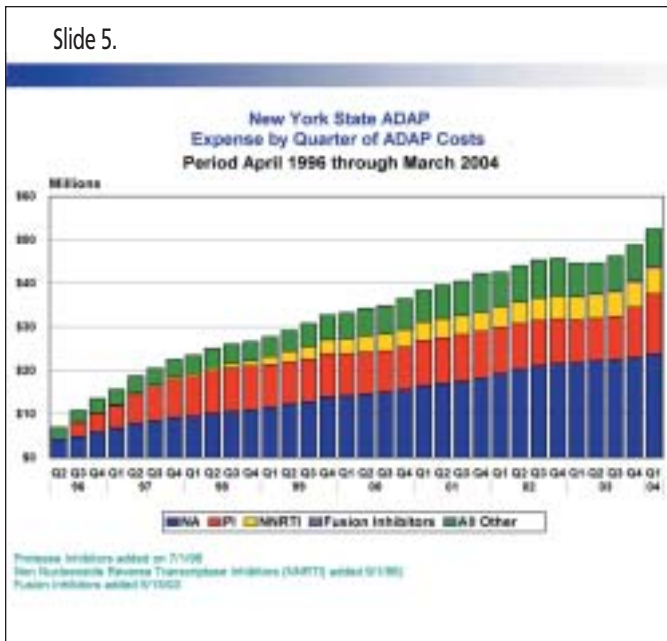
There is an ancillary cost as well with antiretroviral drugs, which is treating the toxicities and side effects. For example, in Slide 4 we took a basket of drugs that we assumed would be primarily used to treat the side effects and toxicity of antiretroviral therapy. You have a big jump in 2000 because we added new categories that we had not added in the past. By 2000, we realized that we were absent some classes of drugs that are needed to adequately care for someone with HIV in the longer term. Relative to the actual cost of antiretroviral drugs per month, it is not a large amount, but it is a cost that is growing and it is part of the cost of treating HIV/AIDS.

Looking at New York State's ADAP costs by quarter from 1996 through 2004 (Slide 5), the nucleoside reverse transcriptase inhibitors (NRTIs) are still the major cost component. The protease inhibitors

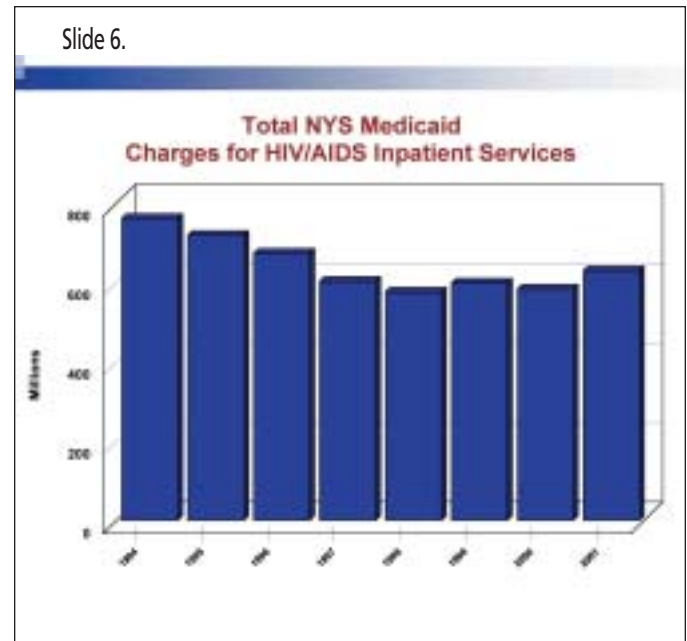
(PIs) are still the second largest. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the new category of fusion inhibitors are third and fourth, respectively, in terms of overall spending on antiretroviral drugs. All of the other drugs, and New York is lucky to have about 450 drugs other than the antiretroviral drugs on its formulary, make up a relatively small part, about 14 percent of total cost. Again, I blame RTV for messing up my charts on average price increases here. We went into cost containment mode the first quarter of 2003 while we tried to get some more money, and we were fortunate that we did, largely from the New York State government. But it really did not have much impact since we could not have any control over the antiretroviral drug end of things, so we had to take the money out of the other drugs.

Clearly we have a growth trend here that is somewhat overwhelming in a relatively closed system such as ADAP. New York State's ADAP, unlike most other ADAPs, also has several other components. ADAP-Plus pays for ambulatory care, medical visits, and lab tests. We have a home care component, and we have ADAP-Plus Insurance Continuation (APIC). We do try and keep people in the private sector by helping them pay for their insurance premiums whenever possible. We did get some savings on home care from 1996 onward when antiretroviral drugs came into play, and we saw a dramatic decrease in home care, but there was little decrease in costs because home care was a small fraction of overall cost. Ambulatory

Slide 5.



Slide 6.



care has more than doubled—it is about two and a half times what it was, but the bulk of that cost is drugs, and the bulk of drug cost is the antiretroviral drugs. So, in a system where we are looking at primarily outpatient care, all we see are increasing costs year after year, month after month.

In New York State, Medicaid pays for the inpatient cost for their patients, and generally for the ADAP patients as well, because by the time they go into inpatient status Medicaid will kick in for them. We can see some of that cost effectiveness that was discussed earlier. In Slide 6 we can see that total Medicaid cost for AIDS dropped from 1994 to 1997 and then started to level off until 2001 when it started to increase again; this is the last year for which I was able to get data. The one thing that I have to point out is that costs dropped from 1994 to 2001 by about US\$200,000 a year. Medicaid's antiretroviral drug bill went up by about by about US\$500 million in that same time period. Even though they were saving US\$200 million in one place, they were still accruing about US\$300 million more in HIV costs at this point, so it is not a net savings, it is a net loss that we are dealing with for government.

It is becoming a harder sell to keep HIV-specific and -related drugs exempt from cost containment measures. Fortunately, our trump card is the decrease in AIDS deaths in New York State from 1990 to 2002. That dramatic decrease in deaths that had started occurring in 1996 and 1997 has somewhat leveled

out now. The result of that decrease, of course, is more people living with HIV—they are living longer, better lives. What you are seeing is that because there are more people now living with HIV and requiring ongoing care and treatment, we are accumulating more and more costs.

So, what is the impact on government and patients? Increasing ADAP and Medicaid costs came at a particularly bad time over the last few years. Both the fiscal situation in this country, and the economy, have not been good. States are suffering a great deal, and it is being reflected in how states are dealing with their ADAPs and Medicaid programs. There is an indirect cost on government through rising health insurance premiums. Michael [Allerton] will deal with that in more detail, I am sure. But from a government perspective, we are seeing individuals losing their private insurance. They can no longer afford to pay those rising premiums, so they are turning to the state programs. There is also a rising cost to government for our own employee health costs, and the impact ultimately on the patients comes by way of the cost containment measures that are being imposed.

Medicaid is focused on generic substitution, preferred drug lists, prior authorization, and reduced pharmacy reimbursement rates. They are trying to squeeze the pharmacies and, ultimately, they are also trying to squeeze pharmaceutical companies with some supplemental rebates by using preferred drug lists. We are very fortunate in New York State; we have probably the

most stable ADAP in the country. When we went into cost-containment mode in 2003, it was around mandatory generics, a limit on the number of refills before the person has to be seen again and issued a new script, prior authorization on selected drugs, and replacement of high-cost drugs with lower-cost alternatives. We reduced the amount of Ambien[®] people could get, and they screamed more about that than anything else. We were very fortunate that ours was more of a tightening rather than elimination. Other ADAPs are much worse off, with capped enrollments and waiting lists.

We are probably going to find that the January 2004 number of 791 people on ADAP waiting lists that José [M. Zuniga] referred to earlier is going to be the lowest number we will see for a long time. States are moving to reduce financial eligibility, imposing restrictive medical criteria, and reducing formularies. I think the most dramatic example of that is New Jersey, which had a full formulary in March 2004. On April 1, 2004, that state's ADAP formulary was downsized to only antiretroviral drugs... So they went from abundance down to a very minimal formulary for treating HIV. We are seeing monthly limits on the number of prescriptions allowed, or the cost per participant. That cost per participant is a particular problem when the drug prices go up, because the cost per person has to be calculated at the front end of what is being paid at the pharmacy, not at the back end of what is the net cost for the pharmacies.

When you use cost containment like that, it is not really fair to the individual patient.

There are some major problems with current government pricing systems. We have a fragmented system with discrete pricing schedules for the various government entities. It is secretive pricing, and it is protected by law. State officials cannot give you the exact price that we are paying. We cannot even know sometimes whether the price that we are paying is the correct price. There are loopholes in the government pricing protections. The CPI penalty that comes into effect if drug prices increase faster than the rate of inflation goes away if there is a new formulation of an existing drug. If the new formulation gets a new code, it starts from scratch and we are only guaranteed that 15 percent rebate. So new formulations, while a really good thing from a clinical perspective, are not necessarily such a great deal for us from a payer perspective, and we find the pharmaceutical industry blocking any legislative attempts to reform pricing.

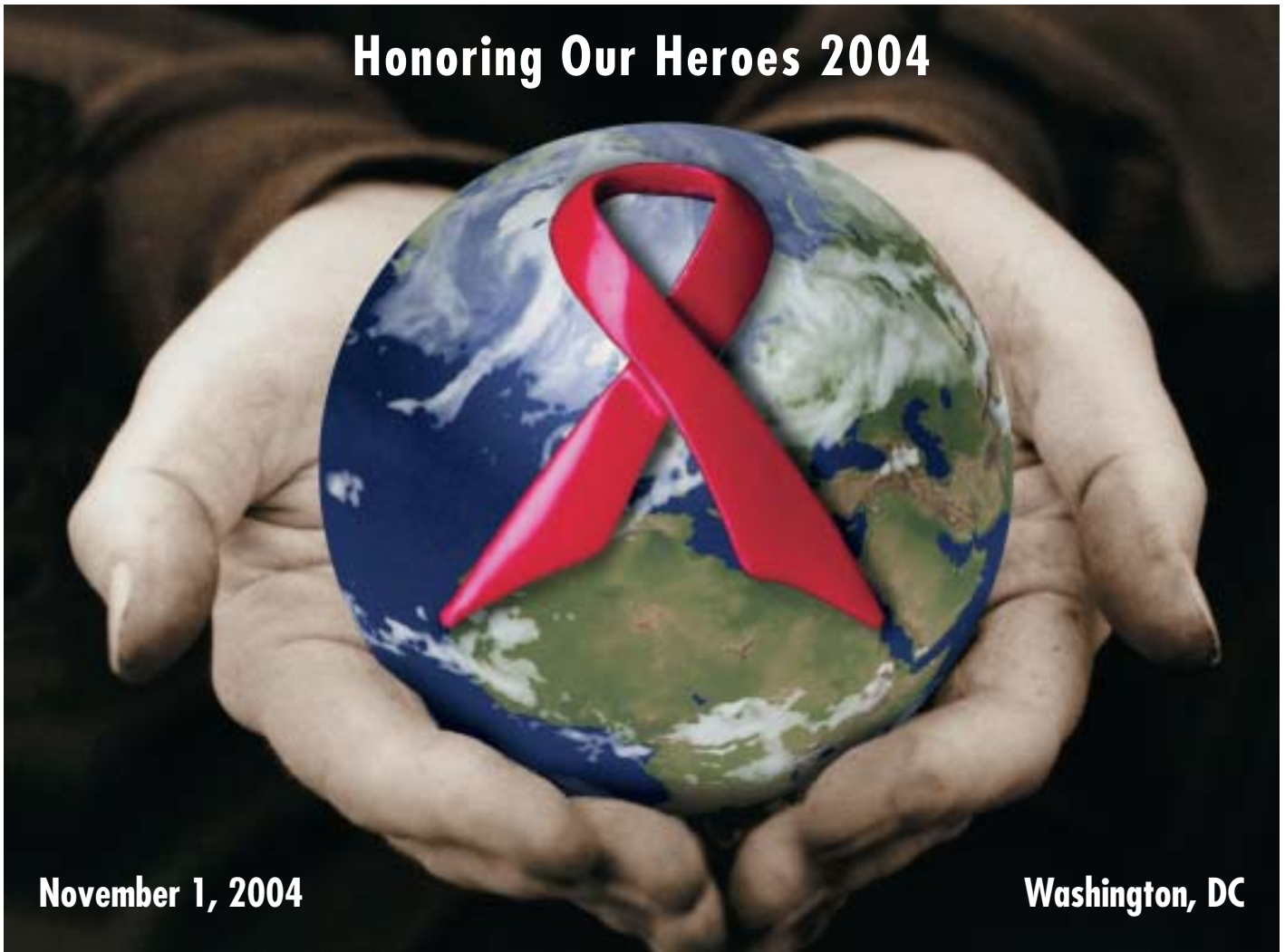
I am very glad to be here with you, and with IAPAC today, to discuss what I hope will be some ideas. There have been some efforts on the part of government and the community to partner around drug pricing. The Fair Pricing Coalition is a coalition of treatment advocates and government payers, which engages senior management of pharmaceutical companies in pricing discussions. The primary focus has been on initial pricing of new drugs and on requesting price freezes from industry. The ADAP Crisis Task Force, which was formed last year, represents 10 ADAPs or AIDS Center Directors, reflecting 70 percent of the buying power of ADAPs. We negotiated pricing concessions with all of the antiretroviral drug manufacturers. We calculated US\$60 million to US\$65 million nationally in savings for ADAPs in that first round of discussions. All ADAPs benefited equally, even though there were only 10 ADAP representatives in the room; one of our major points was that all ADAPs will get a share of the savings. We

coordinate efforts with the Fair Pricing Coalition and other advocacy groups, and we intend to continue to expand our efforts to secure the best possible prices for ADAPs.

You have seen a lot of concise, scientific information about cost effectiveness and quality years of life. Unfortunately, when you are working in government, sometimes the people who are making decisions are only seeing my charts with the big growth lines and the increasing bottom line for government agencies, and that is a problem. It is really dependent upon physicians and treatment advocates to make sure decision-makers get the full picture, but you must realize that often they are looking from a very limited perspective, bottom line tax dollars. How much can we raise taxes and get away with it? How much do we have to cut in order to maintain government as it is? We must play a role in helping them to see the bigger picture. ■

Lanny Cross is Program Manager of New York State's AIDS Drug Assistance Program.

Honoring Our Heroes 2004



November 1, 2004

Washington, DC

Defining the impact of AIDS drug pricing on the private sector



Michael Allerton

Thank you for inviting me to join you today.

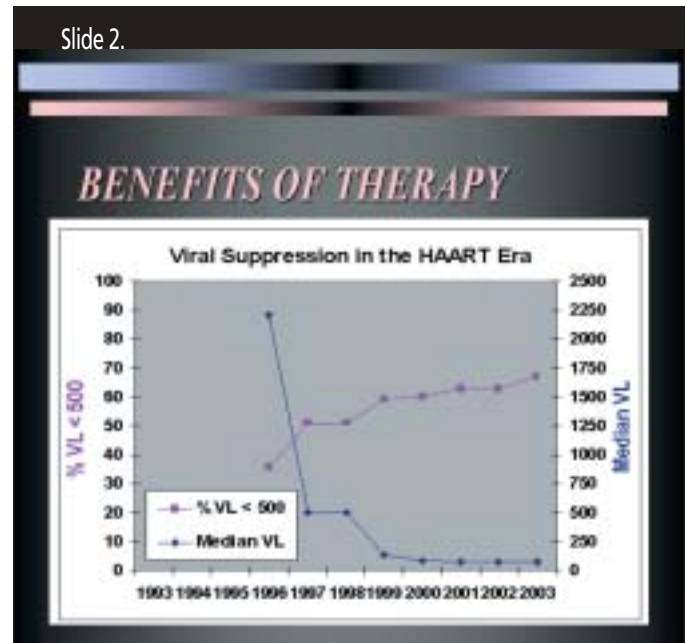
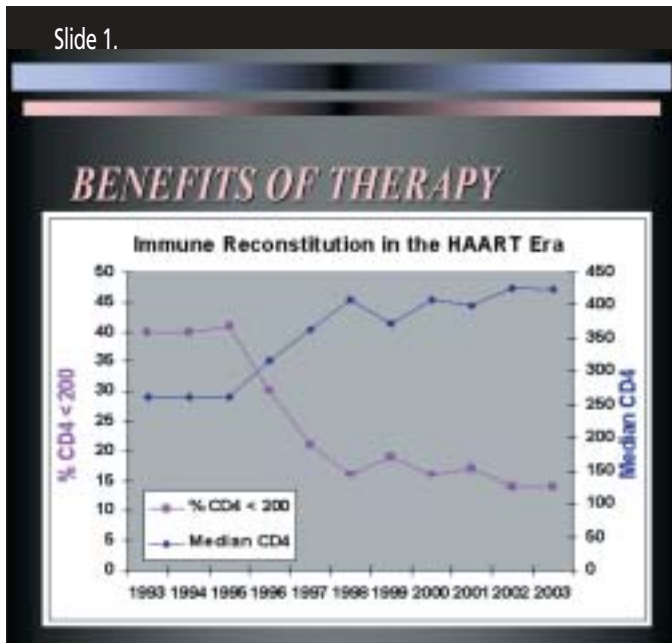
This presentation will take an operational approach to care provision. What I mean by an operational approach is that I want to talk about what I refer to as “being caught between a rock and a hard place” in the clinic on a daily basis. This is not a policy talk in strictly those terms. It is an outcomes-focused talk based on what I am hearing from our providers and my colleagues in the field. Then in closing I would also like to highlight two ethical discussions we now are undertaking that we never had to undertake before. They are very disturbing, and one of them really

relates to the discussion so far today. The other one is sort of “out there.” When I first talk about it you are probably going to wonder, “how in the world does that relate,” but bear with me and I will bring it back to how it relates to this discussion.

I am not a bean counter. I am an administrator, however, the second word in my job description, approved by our human resources department, is “ethical,” the first being “provide”—“provide ethical...” in other words. So, I am not compensated by how much money I save my company. I am responsible for developing appropriate outcomes- and evidence-based procedures for providing optimal care to our HIV-infected population. I really do see myself as an HIV patient advocate that is in the private sector. That is often misunderstood.

I want to give you just a little example of the frustrations that those of us at Kaiser Permanente sometimes have in terms of misperception of who we are and what we do. I am going to go through some demographics and background about the program, but I just wanted to relate to you a story that helps illustrate some of the perceptions about our group. I do not relate this story with any intent to depict any specific organization. I only say, “relate this story,” to demonstrate the perception of the individual who was saying these things to me—not necessarily the views of whom she represented, but her personal opinion and perceptions.

The story is this: I was very lucky in January 2001 to be a civil society delegate to the United Nations (UN) for the UN Global AIDS Response to HIV and AIDS.



As a civil society delegate, I was a consultant representing Kaiser Permanente, and I offered services to the UN on the part of Kaiser Permanente, but there was something very interesting that was different about the United States' representation at the UN versus all other countries. All other countries except the United States enrolled their civil society members into their UN delegations. The United States did not do that, and we only had one meeting with the US delegation, which was held here in Washington, DC, at the US Department of State. It was actually pretty far into the discussions, and because it is the US Department of State, we had to offer our Social Security numbers and our addresses, so I am sure there was some sort of security check and some knowledge base of who we were. I walked into the US Department of State and into this meeting to understand what the collaboration between the US Mission and the civil society delegates was going to be, and a public affairs representative from the US Department of State came up to me, shook my hand and said, "Mr. Allerton, you are from Kaiser Permanente. We are so glad to see industry represented at this." I said, "Well, what do you mean?" She said, "Well, were you one of the delegates that was recruited by..." and then she named a major pharmaceutical company. My first reaction was, "No, I am surprised. I did not realize that company was negotiating to have civil society representation at the UN." She said, "Well, I am very concerned that the

delegations will be overtaken by advocates, and that the importance of business will not be understood." I said, "Well, you have to understand that I come from Kaiser Permanente. We are a not-for-profit prepaid health plan." Her response to me was, "Oh, come on, you sell insurance." Well, we do not sell insurance. I do not sell insurance. I am part of the Permanente Medical Group, and I think that is a good example of the misunderstanding of the not-for-profit private sector.

I have spoken to colleagues who are in Blue Shield, which in California is also a not-for-profit, and we have some of the same difficulties. I cannot speak for the for-profit industry, and it would be interesting to see what their perspectives would be, because I am sure theirs might be a little different from mine. This example was just my way of qualifying what Kaiser Permanente is from a personal level, and explaining the frustrations regarding some of the common misunderstandings. I hope that helps to provide some perspective as I continue.

Kaiser Permanente is a national medical care program. We are in nine regions across the country. Most of my statistics are going to be combined for northern and southern California. The set-ups are slightly different in some of the other regions, but overall we provide care for over 8 million members and 14,581 of those are HIV positive... The average length of time those individuals have been in the health plan is eight years prior to

diagnosis. So, we have a very stable population and they tend to stay with Kaiser Permanente. They tend to be very satisfied with Kaiser Permanente and the quality of care that they get, so we have very good longitudinal data for outcome measures and research purposes.

I am from California, and I am going to talk about California and some of the unique things that have happened there in the last few months. It is important to understand that the total HIV patient population is just under 10,000, but if you look at the total California membership, we have a seroprevalence rate of 0.16 percent; that 0.16 percent of our total patient population accounts for our second highest pharmacy cost, second only to depression. With costs like that, we are going to be concerned.

I do not have to preach to this group about the benefits of therapy, but I thought it would be interesting to look at just our specific population. Slides 1 and 2 show just the northern California population database registry results. As you can see, we have certainly had the same marked benefit of antiretroviral therapy that has been seen everywhere else, both in terms of viral load suppression and immune reconstitution. Viral suppression is probably one of the most amazing pieces. You see here measures for viral load suppression. The viral load under 500 copies/ml is what was used as a measure until 1998, because that was what the levels of detectability were for the first few years of this evaluation. The reason why the dark

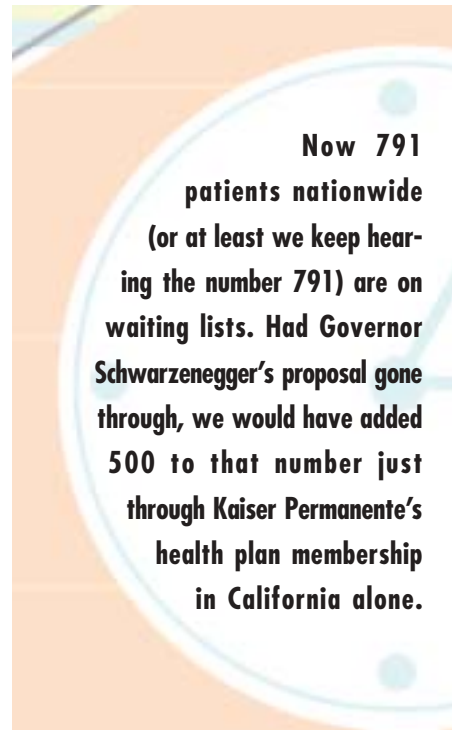
diamond bar goes much farther below 500 copies/ml at a certain point is that in 1998 we changed assays and were able to go below 500 copies/ml as a detectable level.

Another amazing statistic from Kaiser Permanente is that the mortality rate of the HIV/AIDS cohort has been less than 1 percent per year for the last six years, and that mortality statistic includes all fatalities, so some of those individuals were killed in car accidents or died of heart attacks, etc. Another statistic that I think is also extremely important is that in northern California, viral load is below levels of quantification for 72 percent of all of our members who are on therapy. I think that it is very clear that highly active antiretroviral therapy (HAART) is high-cost but extremely high-benefit for our members. But given that it is high-cost and high-benefit, we have three major concerns. First, how are quality and efficacy assured? Second, how do we maintain numbers like that? And, third, ultimately who pays?

I am going to answer the third question first. Obviously, private purchasers, entitlements, and AIDS Drug Assistance Programs (ADAPs) pay, but I want to talk about some unique aspects of each of these. Increasing numbers of private purchasers over the years have instituted caps and limited pharmacy benefits. It is really important that people understand that this is purchaser driven. Kaiser Permanente does not decide how much we are going to pay, it is the purchaser who buys Kaiser Permanente as insurance that dictates to us more and more that there will be high caps and high co-pays. What we are seeing is that there is an increased need and demand for new product lines. Those new product lines mean we need to reach and provide coverage for the young, healthy individuals, and they do not want to subsidize everybody else. I firmly believe that this is going to backfire in a few years.

For now, anyway, we have plans that are being paid for by purchasers such as Bank of America, Wells Fargo, and General Motors. They buy health insurance or premiums through us with, for instance, maximum drug coverage of US\$1,200 to US\$2,000 a year, or US\$50 co-pays to the emergency room, or US\$200 a day co-pays for hospitalization. These plans are very attractive to that young, 20-something family. But I think the first time that

family, which may now believe that their health is benefited more by their membership in a gym than their membership in an insurance program, is going to be sorely woken up is when they have an infant who is born with a heart defect and needs open-heart surgery, and they are going to go bankrupt because they will not have insurance. The headlines are going to say, "Kaiser Permanente refuses to do open heart surgery." But the reality is that they or their employer have not purchased a plan that is going to cover that possible medical crisis. The demand for these new product lines is very disconcerting to me.



Out-of-pocket expense caps are also happening. There is a sort of middle ground. You only have US\$2,000 worth of medication coverage, but if you spend US\$5,000 out of your own pocket, then you go back to having drug coverage. So there is a maximum out-of-pocket expense for some of these plans that, if met, leads back into the insurance coverage. Where that is a real problem is within the ADAP. I firmly believe that in the public sector an ADAP patient tends to stay an ADAP patient, and in the private sector people rotate through ADAP. They are in it, they are out, they are in, they are out... I will speak about the problems with that scenario soon.

Issues with Medicare, Medicaid, and medical Supplemental Security Income (SSI) were significant for us this year.

Many of you know that Medicare does not reimburse for name-brand drugs. They have carved out life-saving drugs such as chemotherapy, but they have not carved out AIDS drugs from that exclusion, and this is very important. It is very ironic that our oncologists, when they hear this, are very supportive of the HIV providers. They say, "Antiretrovirals have a better track record than chemotherapy agents." But we continued, even though there was no reimbursement for name-brand drugs, to reimburse them until January 1, 2004. Just from a competitive standpoint, we could not continue to do what nobody else was doing, so as of January 1, 2004, all of our Medicare and SSI patients lost any kind of name-brand drug coverage for HIV.

To cope with this, we did some proactive planning. We knew that at any given time, we have a number of patients who are enrolled in ADAP. We knew that there was going to be a sudden increase in those patients who are eligible for and require ADAP assistance, and so we hired some temporary case managers. Through pharmacy records, they identified those individuals, about 500 in the State of California, to make sure that their paperwork and everything was completed in time to enroll in ADAP starting January 1, 2004. At exactly the same time, the new Governor of California, Arnold Schwarzenegger, announced the proposal to freeze all new ADAP enrollments starting January 1, 2004. So we were caught again between a rock and a hard place.

The main ADAP stability issue, of course, is whether it is going to be there, and whether it is going to become capped. In California, we had slightly under 2,000 people living with HIV/AIDS, or 20 percent of our members, enrolled in ADAP in the fourth quarter of 2003. Approximately 500 new enrollees were eligible January 1, 2004, because of the generic versus non-generic exclusion. Now 791 patients nationwide (or at least we keep hearing the number 791) are on waiting lists. Had Governor Schwarzenegger's proposal gone through, we would have added 500 to that number just through Kaiser Permanente's health plan membership in California alone.

I think the stability of ADAP is very important. It is also extremely important for the private sector to remember that it is not always the same 20 percent. That rotational issue has a profound impact on

day-to-day operations. Our case managers are telling me that they used to spend time with our clients and our members talking about adherence strategies, developing pill-taking methodologies, and loading trays. They now spend the majority of their time just trying to find out where patients are going to get their drugs. It is a different role for them than what they were originally hired to fulfill. Also, the issue of whether there should be a freeze on new enrollees in ADAP is going to mean that a lot of patients are going to drop out of, forgo, or abandon other coverage just so that they will not lose their slot in ADAP, which ultimately will cause the cost of ADAP to go up.

Now, I would like to tell you a little bit about our model of care, and how quality and efficacy are assured. We do not talk about the best bang for the buck, we talk about the best bang for the pill, and how we can assure the most appropriate utilization of the drugs that we prescribe. The knowledge and abilities of care providers for HIV is a critical component. In California, we defined an “HIV specialist” for our organization long before the American Academy of HIV Medicine (AAHIVM) came up with their definition for the United States, and ours was actually much more stringent. The AAHIVM’s definition is actually quite thin, so once the AAHIVM came up with a definition, all of our HIV providers immediately qualified.

We defined HIV specialists, and we moved our care of HIV patients to specialists. One of the ways we did that is a gate-keeping mechanism around the initiation of therapy rather than around drugs. A pharmacy will not fill an initiation of antiretroviral therapy unless it is written by one of our HIV specialists. The concern here, of course, is that a general internist who may be working out in The Valley, and may have had one or two HIV patients, could be reading that the most effective new drug is enfuvirtide (ENF). We certainly would not want them to initiate therapy on a new patient with ENF. Although that would likely not happen, we certainly want to make sure that something similar to that does not happen, thus the heavy reliance on HIV specialists as we define them. Kaiser Permanente in California is really the HIV specialist model. We now have 88 certified HIV specialists in northern California by our criteria...

We also do heavy monitoring. One of our quality control measures is CD4 counts and viral loads on an ongoing basis, basing the frequency of those tests on clinical guidelines. We also do resistance testing for initiation and for any change in therapy. Again, part of the reason we rely on the HIV specialist is to interpret those tests.

What are the implications for physicians and members? I would like to give you an anecdote. In an earlier presentation today you met an HIV patient named Bill. I would like to introduce you to Sarah. Sarah is a 63-year-old female. She was infected by her husband, who was infected by a blood transfusion given to him during a total hip replacement. She is an ADAP patient. She is a Medicare patient. She is not Medicaid eligible because she has an Individual Retirement Account (IRA) and the amount of that is too great for her to qualify for Medi-Cal, which is what we call Medicaid in California. She has been in our Medical Financial Assistance (MFA) program for six months—this is a private charity that is within our organization. The social workers and case managers have access to MFA funds to help patients who get caught in situations where they cannot afford their care. In the past, it was used for things such as durable medical equipment, but now it is being used more and more for pharmacy. Sarah exceeded the limit because MFA is only eligible to a member for six months, and she was on it for a full six months. Her AIDS drugs are covered completely by California’s ADAP, but she and Bill are good examples of people with co-morbidities. She also has significant cardiac problems and none of her cardiac medications are covered at this time. These medications were being picked up by MFA, but now they are being paid for by her church. It was the social worker who went through the gymnastics of finding a charity like her church to get those drugs covered. Again, it has a real operational impact because those people are best employed working with our members around other issues, rather than trying to make phone calls to find dollars.

Another impact is that although the cost of drugs is not a factor integrated into the clinical guidelines, adherence and the ability to adhere is part of the clinical guidelines. I am hearing more and more concern from providers about initiating

therapy that will then have to be stopped because of cost factors that are being borne by the member. An example that was given to me by one of our physicians was of a hypertensive diabetic patient who, every December, stops taking his hypertension medication and his diabetes oral hypoglycemics because his property taxes are due. He knows that once he pays the property taxes in January or February, he can start picking up his medication again, or otherwise he will try to spread it out during that period of time and make a 30-day pill supply last 60 days by taking his medication every other day. If a physician has the idea that an HIV patient might be thinking of this strategy with his/her antiretroviral therapy when December rolls around, I can guarantee you that, if truly qualified, that physician will not be prescribing antiretroviral therapy, because the consequences of interrupted therapy not only for the individual but for the public health are significant.

One of the reasons I stress the fact that 72 percent of our patients on antiretroviral therapy have undetectable viral loads is that it has an impact on transmission. So we are not only talking about the quality of life of the individual, we are also talking about arresting the epidemic through medication. I have already mentioned that the case managers and other allied health professionals are spending more and more time dealing with these issues, but I think it is only going to get worse. I have a couple of ideas for solutions; they are perhaps not solutions, but they are things that we have done with success.

One is certainly clinical trials. Clinical trials have been a boon to our pharmacy costs. We do a significant amount of clinical trials in California. We were five of the ENF clinical trial sites in northern California. What that meant was that our five medical centers that were ENF clinical trial sites were disbursed geographically enough that every health plan member in northern California had access to the then-investigational ENF. That benefited us because we got that drug free, and the patients who needed it and met the criteria got that drug free, and they got it earlier than they would have otherwise. Their cost savings continued because even after it was US Food and Drug Administration (FDA)-approved, we were getting free drugs for a period of time. That was a short-term cost offset

that was very beneficial. The downside, however, is that we have never recovered our cost of clinical trials, outside of pharmacy costs. There are costs for just the FDA regulation and management of the records and the clinical trial nurses. Some of you who do not live or practice in California might be surprised to know that a Clinical Trials Registered Nurse (RN) in the San Francisco Bay area—because of skill, demand, and union contracts—makes more than a general internist in many other parts of the country. When pharmaceutical companies come to us with an operating budget that is based on a national average of cost per full-time equivalent (FTE) for an RN, we never recover those costs, not in California anyway.

The other piece is treatment Investigational New Drugs (INDs), which are certainly a boon to us, but again, the time commitment of providers on treatment INDs is significant. The cost to go through the Internal Review Board (IRB) is not insignificant, and is not usually thought of as a direct cost. I sit on the IRB, so I know what we have to review, and the cost for us to do those reviews is not insignificant.

The last thing that I want to mention as an idea for a solution, is something that I have already seen right here through this treatment coalition that is gathered. I am really glad to see you folks, but I must say that I am definitely not a person who openly advocates civil disobedience, especially having once been handcuffed by ACT UP. I definitely do not advocate civil disobedience. However, I have to tell you that there is a significant role in advocacy today, and in conveying strong messages. In 1996, when viral load tests were not yet FDA-approved, our New Technologies Committee was absolutely adamant that they would not cover viral load testing when it was becoming the standard of care on the West Coast. It was not an issue on the East Coast, ironically enough. It was, however, a major issue on the West Coast. Our New Technologies Committee changed their minds the day after ACT UP delivered coffins to the Kaiser Permanente Board of Directors. I think that is quite an interesting little comment on the juxtaposition of an activity and then a change of heart, so my biggest concern is the visibility of the advocacy effort and where it is these days.

I mentioned two ethical questions that are being posed for us on the horizon. The first one is: “Adverse selection, and is that an issue?” The second one is: “What is the moral imperative for post-exposure prophylaxis (PREP)?”

I was asked this question just the other day by one of the providers: “Have we reached a point where it is no longer socially acceptable or economically viable to do the right thing?” What did he mean by that? I have already told you that we covered the name-brand drugs for a year longer than they were reimbursed, that we have MFA so that patients can get their needs met. We also have case managers who break their necks on a day-to-day basis to find out how patients are going to get their coverage. We feel that we have a moral obligation to those health plan members who have HIV, to make sure that all their needs are met, but since we do that and nobody else does, when the playing field is not level we may not be able to sustain economic viability if we continue to do many of these things. Where does the social acceptability come in? In California, we had a multiple month strike of one of our major purchasers, the grocery clerks in southern California, who wanted cheap, affordable healthcare. They do not want to accept carrying the costs of a sicker population. They want the rating based on their own utilizations. We are getting pressure from both directions, and I think this is probably the most disturbing question I have heard in my lifetime at Kaiser Permanente, that someone would actually think that we may have reached a point where it is no longer socially acceptable or economically viable to do the right thing for our patients.

Now, let me discuss the ethical issue around PREP. We know that one of the most important advances in curbing the AIDS epidemic would be an efficacious vaccine. But in the absence of an efficacious vaccine, other strategies are being examined, one of those strategies being microbicides. This is especially important when you think about the disenfranchised female population on a global level that is at continued risk for HIV infection with no social ability to practice any kind of safety mechanism. So, in the absence of a vaccine and/or a microbicide, the Bill & Melinda Gates Foundation and others have said, “What if one of these antiretroviral medications, taken on an ongoing

basis in low doses, would prevent infection?” It sounds wonderful, but I have to tell you there is a lot of skepticism, and there is going to be a lot of fallout on an international level.

At the 12th World AIDS Conference in Geneva, a representative from the San Francisco Public Health Department presented a proposed study on PREP for non-occupational risk categories, and there was a flurry of negative, adversarial, downright confrontational questions that came from other parts of the world. The questions were along the line of: “We are talking about a non-occupational exposure and providing drugs to individuals in a wealthy environment who do not have this infection, when the vast majority of the world which does have this infection cannot get medications?” Now the argument may be made that if we sell more of these drugs in the United States, pharmaceutical companies may have more resources to give lower prices elsewhere. There is not any given answer to this, but the whole issue of providing pills, at least in this country, to an uninfected population whose members can prevent infection by other means, when this medication is not available to HIV-infected people in other parts of the world, could have tremendous fallout.

These are the sorts of conversations that are being undertaken today and will become even more important in the future. There are a lot of skeptics. The first thing one of the physicians at the Geneva conference that I referred to said when he heard about PREP was, “My, what a way to sell more drugs. This must be sponsored by a drug company.” Of course, he is much more cynical than I. But, again, I think that is one of the issues that we have to deal with, and we would not be having these conversations if these pills cost the same as aspirin. Those are some of the discussions that are happening in the private sector, some of the dilemmas that we are facing, and I really believe that it is only going to get worse.

Thank you very much for the opportunity to let me get that off my chest, and I really appreciate the honor to be able to be here today to with you and with the International Association of Physicians in AIDS Care (IAPAC).

Michael Allerton is HIV Operations Policy Coordinator at the Permanente Medical Group at Kaiser Permanente.



A physician's call to action

Benjamin Young

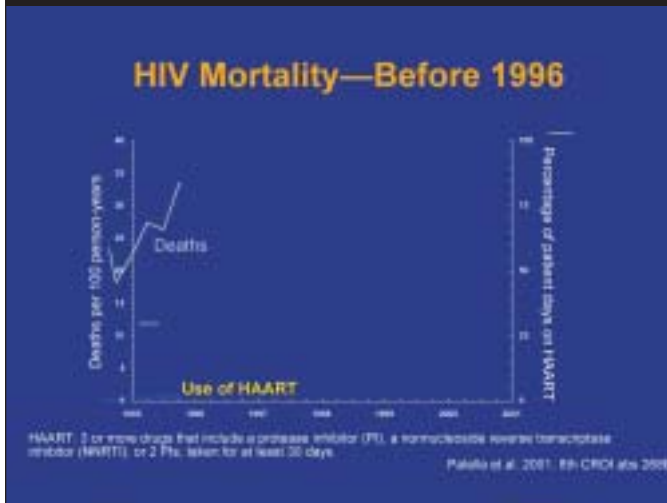
As a doctor and a member of the HIV treater community, I am truly privileged to be here; I am really quite honored to be invited by the International Association of Physicians in AIDS Care (IAPAC) to speak on behalf of both my colleagues and, more importantly, on behalf of my patients. I want to point out, because we have some representatives of the pharmaceutical industry here, that my beliefs on this topic have been labeled as “lunatic,” have been labeled as “fringe,” as “minority.” I would challenge you to consider whether these ideas represent the ravings of a lunatic, or if they should represent the mainstream opinion, or do

represent the mainstream opinion, of real-world HIV doctors. So on behalf of my patients, again, I thank you for this platform.

I am going to frame our discussions today in a historical view, which is necessary in order to issue a “call to action.” This is a discussion that is focused on the domestic problem—a problem which, frankly, receives very little attention. We talk a lot about global AIDS. We talk a lot about the South African problem, the Botswana problem, the problem in South Asia, and those are undeniably big problems. In all of the challenges of dealing with the global AIDS problem, and, simultaneously, with all these successes that we have seen in care in the developed world, we have allowed ourselves to think that the problem has been licked. The pictures of people climbing mountains, the pictures of Magic

Johnson, who looks terrific, who is terrific, mask or hide the magnitude of the problem. The problem is the nearly 1 million people living with HIV/AIDS in North America, that in a sense I represent, at least half of whom do not have publicly insured mechanisms for AIDS drug access.

Before this looks like some sort of tirade against the pharmaceutical industry, I would like to say I am also a member of the research collaborative called the HIV Out-Patient Study (HOPS) cohort. I am proud to share data that reflect how far we have come in such a short period of time. This is from Frank Palella’s now very well quoted research, which was published in the *New England Journal of Medicine* (Slide 1). The research looks at the mortality of patients with HIV in the United States. This is looking at patients with AIDS,



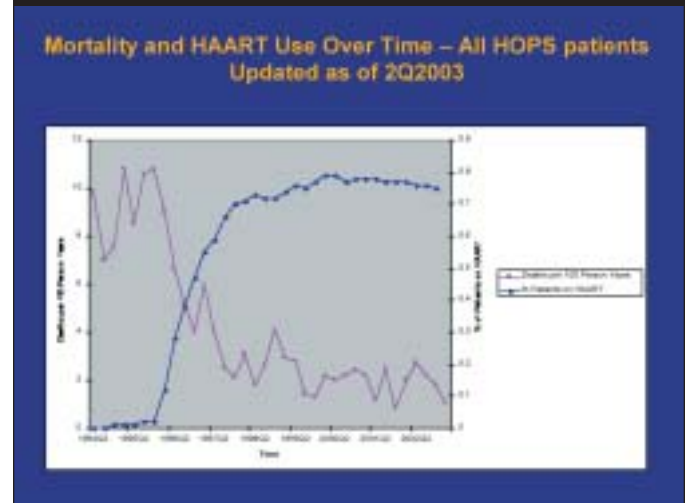
actually a cohort of patients who had CD4 counts less than 100 cells/mm³ at any given time. Back in the pre-HAART era, the pre-protease inhibitor (PI) era, or the pre-azidothymidine (AZT) era, the death rate in this population was about 30 per 100 person-years, and a crude statistical version of that statement says that about a third of the cohort was dying every year.

Something magical happened, of course, to end that era. In those days, of course, an HIV diagnosis was equivalent to having AIDS; you were inevitably going to progress to AIDS and were therefore going to die. As everybody said, the expected survival was about three years. So antiretroviral medications in that era in fact had very limited value. There was some debate, of course, over whether they were useful or not, and in that era in the United States, 30 percent of babies born to infected mothers acquired HIV. Young fellows like me, at the time, became experts not in the treatment of HIV per se, but the treatment of multi-drug resistant *Mycobacterium avium* complex (MAC), multi-drug resistant cytomegalovirus (CMV), and multi-drug resistant candida.

Again, because of the investment of millions and billions of dollars, and the investment of hundreds of thousands of patient lives and hundreds of thousands of investigator hours, the death rate changed dramatically, as shown in Slide 2. This figure shows Frank Palella's most recent figures from the HOPS cohort. The numbers have changed somewhat because we are

not looking at just the AIDS patients; we are looking at the entire cohort. This figure shows all patients with HIV in the HOPS cohort. This represents about 7,000 patients in eight cities, in 10 clinics around the country—an ethnically, demographically, and socioeconomically diverse cross section of the US population. This shows that the death rate has declined. It has plummeted, and it remains down even up to the last quarter of 2003, and the use of highly active antiretroviral therapy (HAART)—defined as a multi-drug, multi-class regimen—has increased to a significant proportion of that patient population. Deaths are down.

Slide 3 shows us that the rates of complication also remain down, despite the fact that preventive measures really have not changed dramatically in this era. Medications and the investment of pharmaceutical companies, the investment of patients who volunteer for clinical studies, the investment of advocates who have pushed us all for access to care and cheap medications, have accomplished this for us, and this is a tremendous evolution in the care and the prognosis of this particular treatment population. Another challenge is to realize that these advances have important implications for the entire issue of drug discovery; what we can do if we simply apply force, if we apply will, and if we apply money. It is an incredible revolution. So, medications save lives. Investment in medications saves lives. Investment in drug discovery, investments from advocates have saved lives.

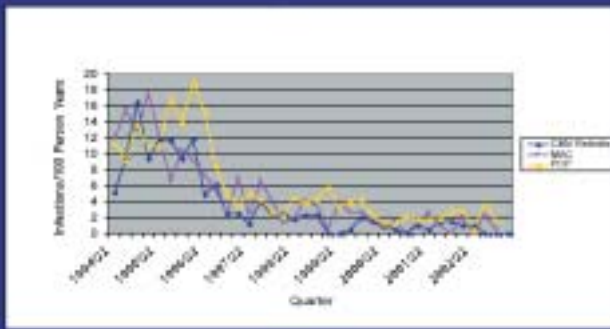


The current armamentarium includes 22 antiretroviral drugs; 19 distinct drugs and three fixed-dose combinations. It is an incredible tour de force, and compliments to everybody who helped us get this far. The lives of my patients and the lives of your patients, the lives of your clients, your communities, and your customers all benefit from this achievement. These numbers just include drugs that have been approved since 1996, the dawn of the HAART era. In the future we will likely see new co-formulated pills, new classes of medications, perhaps CCR5 entry inhibitors, perhaps a GP120 entry inhibitor, perhaps an integrase inhibitor. The point is that drug discovery will continue if we find ways to continue to provide incentive for that.

We are also in an era where we are talking about the potential for novel strategies, and novel strategies are driven in part by toxicity issues, but also in part by cost issues. I think it is important to bear in mind that those will also impact how we approach treatment strategies in the years to come. I would like to bring this back to my hometown (Slide 4). In Denver, we currently have 8,000 patients with HIV, according to data from the Denver Department of Public Health. Data show that we have saved over an estimated 2,000 lives out of the 8,000 patients who are running around in our state right now. In our little town we have also done a pretty good job of preventing mother-to-child transmission of HIV. There have been four babies born with

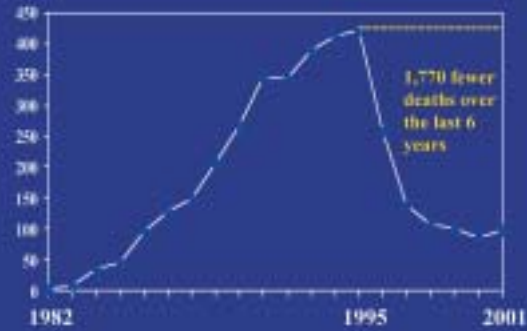
Slide 3.

Opportunistic Infections over time among HIV patients with CD4 < 100
HOPS Data Updated as of 2Q2003



Slide 4.

HIV/AIDS Deaths in the Denver Metropolitan Area, 1982-2001, including the HAART era 1996-2001



HIV since the beginning of the HAART era, and three of those babies were born to mothers who were diagnosed post-partum. In the case of the one baby who was born to a known patient, that mother was diagnosed in 1996, in the early AZT era.

What we can do if we get this right? We can save lives. We can improve quality of life. We can prevent HIV infections. The stakes are not just profits. The stakes are not whether or not I get reimbursed. The stakes are lives, and that is something that I think we should not forget. When we talk about policy, when we talk about payer mix, when we talk about fractional shares of market, or new prescription drugs; what we are really talking about is whether people live or they die. In the HAART era, HIV does not mean AIDS and it does not mean death. The average survival of a newly diagnosed HIV patient is probably calculated in decades, not years. In fact, when I counsel new patients, I tell them that they are going to live for decades, live to be old men or women, live to see their children graduate from college, talk about retirement plans. Antiretroviral drugs, of course, in this era have significant value, because we can prevent HIV and AIDS not just in the United States, but elsewhere.

Now we are experts not just in treating complications of AIDS. Actually, I have not seen a case of CMV in five years. So now we have become experts in managing antiretroviral therapy. Mortality is down and, in fact, as was presented at the 11th Conference on Retroviruses and

Opportunistic Infections (CROI), the causes of death in our HIV population have also shifted from traditional AIDS deaths to non-AIDS causes of mortality—cardiovascular disease, non-AIDS malignancies, liver disease. In my practice, the leading cause of death now is suicide because of my patients who have had ongoing psychiatric issues, but not *Pneumocystis carinii* pneumonia, not MAC, not wasting.

The problem, however, is that the new incident cases continue. On this issue, we have not done a very good job at all. In fact, we have done a terrible job as providers, as educators, as industry, in preventing new cases, because the message has been forgotten. We have dropped our guard. We have become complacent with regard to HIV. We have become complacent with regard to prevention, and that means now that more women, more heterosexuals, more people of color, more people who do not speak English are acquiring HIV, and that provides further challenges to us as a treatment community in providing care and access to care. As this demographic changes, it becomes not just an interesting epidemiological point but, in fact, an ethical imperative to address the concerns of the changing demographics of our population. The consequence of this success in therapy, as Patrick [Clay] alluded, is that patients live longer. That is a good thing, because that means we allow people to live life without having HIV as the veneer through which everything else appears. It also comes with some costs. The costs are

long-term treatment, long-term engagement with medical care, long-term issues with long-term toxicities, and the long-term financial and physiological costs of having HIV and its therapies.

What we have seen in the last decade, which is about the period I have been providing HIV care, is an unprecedented evolution, and arguably revolution, in the care in the medical industry around HIV. Again, in Colorado we have, roughly speaking, 8,000 infected individuals. About 4,000 of these individuals are on antiretroviral therapy. Our AIDS Drug Assistance Program (ADAP) is bankrupt, with ever-increasing demands, with about a 5 percent growth in ADAP requests per year and flat funding over the last three years. A year ago we had zero patients on our waiting list; we now have 220 patients. Twenty-five percent of the people on the national ADAP waiting list reside in my little state.

There are also challenges ahead. These challenges present ethical, moral, and medical issues for us, such as the ever-increasing prevalence of primary transmitted drug resistance, an increasing prevalence of pre-existing drug resistance, the increasing prevalence of resistance in patients who are already under care. In my state, a decreasing amount of physician reimbursement has led to the closing of three of our large family practices that provide specialty HIV care.

So, what does the future hold? This is the “call to action” part. My view of the future is that HIV and AIDS will ravage

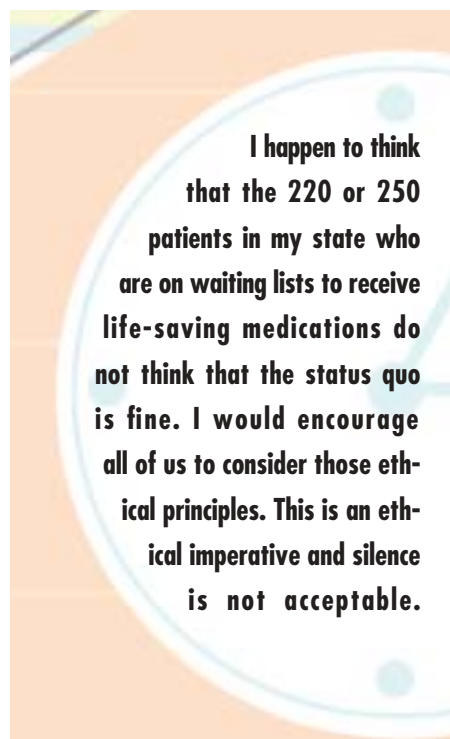
the developing world. If you want to visit South Africa and you want to go on safari, do it soon, because the face of southern Africa, the face of East Africa, and the face of Asia will change irreversibly in the decade to come unless we get off our butts. In fact, the differences between the haves and the have-nots will only increase in the decade to come. In the developed world, there will be more patients living with HIV, and the increasing frequency of either transmitted or existing drug resistance, and, therefore, there will be increasing and significant need for medical and medication support. Unless we get off our butts, these problems will not improve.

There are a couple of potential views on the future of medications. I think medications will become less expensive, certainly AZT is going off patent, which will help in that regard. We are already seeing a dramatic trend toward easier-to-take medications. I think new medications have made a significant change in my patients' ability to adhere to their regimens, and thus increased their quality of life, and I think that investment was worth the time and effort, though maybe I am biased. However—this is the big “however”—I think recent price changes really challenge our resources and challenge the way that we must think about how we deliver care not only to this population, but also to other patient populations. I do think we have a dramatic problem with our public policy at times, and sometimes that public policy is downright irrational. Because of these issues, I think it becomes an ethical imperative for us as physicians, whether we work in industry or the public sector, to consider the ethical principles involved in these kinds of issues. I have been called a lunatic because I think that there are ethical principles that should guide opinion around these points.

I do believe that we will see some of these new drug classes actually make it to the market, and these will offer unprecedented hope for patients who right now do not have hope. I think back to the 1997-1998 era, to patients who had multi-drug resistant virus and are now dead; only wishing that they could have seen a glimmer of hope for some of these new medications. Once again, I value and welcome the support from the pharmaceutical industry in bringing these new drugs forward.

I have alluded to this before, but I think that there will be new strategies to

administer therapy that will decrease total drug exposure and decrease total drug cost. Again, this poses some difficult questions for the pharmaceutical industry in terms of creating an incentive for profit, but it also provides us a way of providing care and access to care to people who might not otherwise be able to afford it. Unfortunately, there will be no cure in my lifetime, and my fatalistic prediction is that there will be neither a therapeutic nor a preventive vaccine in the next two decades.



We have to stop hoping for these kinds of handouts and start making some choices, or at least have a voice around these choices.

This “call to action” is based on the principle of an ethical imperative to save peoples' lives. Prevention strategies have to improve. This means that the Bush Administration has to forget about the idea that condoms increase abortions, and think about the ethical imperative that has been demonstrated in country after country—that condoms and latex save lives. Latex prevents HIV, and this runs counter to the Bush Administration's healthcare policy. This runs counter to the Vatican's policy. That must change, and doctors have to stop being quiet and acquiescent on that point. This has been a discussion that might otherwise seem to have an anti-pharmaceutical industry slant, but continued investment and continued

profit for the pharmaceutical sector is the key to further drug discovery, and that must be fostered in a way that is productive.

As physicians, we must begin to consider the mechanisms for overcoming barriers to access to care. This is the key issue. In fact, access to care does not just mean medications, it does not just mean condoms, it does not just mean latex, but it also means appreciating the very complicated issues of the political, cultural, and economic climate in which all of this is delivered. Our failure to appreciate that during the 13th International AIDS Conference in Durban, South Africa, contributed to the continued intransigence of the South African government, preventing access to care. If we get it right, we can do something that is really unprecedented, which is that we can save lives around the world. We might be able to change the way that governments and cultures around the world interact with one another. But doing that is going to require unprecedented collaboration between all sectors—between government and nongovernmental organizations, between community and industry, and between patients and doctors.

I think we are standing at the precipice where we might be able to do that. Ironically enough, this possibility may have been triggered by Abbott Laboratories' decision to increase the price of ritonavir (RTV). In a sense, we owe Abbott Laboratories a little scintilla of gratitude for catalyzing that discussion.

It is an ethical principle based on ethical imperative. I was very fortunate a week ago to get my 10 minutes of audience with Archbishop Desmond Tutu when he was coming through Colorado lecturing on AIDS, drug pricing, and access to care. He articulated something that I would like to use as a framework for thinking about how to move forward, and I am afraid I will completely destroy his words. But he talks about taking care of family. Family is not just your genetic family or your first-degree relatives. Family is the entire planet. It is the entire community. I used to do a lot of volunteer relief work in Guatemala, and we talked about *comunidad*, which does not just mean community, it encompasses a very large sense of caring both for people you know and people you do not know. I would like to pause at the idea that we must consider the possibility of *comunidad* and family in our communities. HIV communities are

defined broadly as industry, the government, the research community, the medical community, the patient community, and the activist community. The question really is, "If you view the other members of that community as your family, are the strategies that you are developing consistent with how you would take care of your grandmother?" If the answer is yes, then you are proceeding on an ethically sound principle. If the answer is no, the next question is whether you should reconsider that policy.

HIV patients are not patients who have allergic rhinitis, and while the pharmacoeconomic principles that guide drug discovery often are used to explain pricing strategies and discovery principles and other treatment niches, I do not think those principles necessarily apply. HIV is a life-threatening disease. HIV therapies in a diverse formulary for HIV medication save lives and clearly improve quality of life. So the models have to be re-thought. We need to challenge the way that we think about this, and I challenge the pharmaceutical industry to rethink, consider what we are doing here. Can we do something which is proactive and creative, and which can actually change the entire healthcare industry for the better?

I believe very strongly, although it is debated, that access to life-saving care is not just a good idea, not just something that makes money, it is actually a human right. That may seem a radical idea, but in fact it is not. Unless the idea is established in our principles that access to care is a human right, guys such as me get labeled lunatics. I happen to think that it is not a lunatic idea that access to care is a human right, and I would like to think that physicians who believe so are not lunatics and are not representative of the fringe minority. That said, access to profit is probably also a right. If

you subscribe to capitalism as the engine by which we get new medications, the engine that stimulates discovery, then that is an important right. But that right has to be balanced against the other right, and those are the difficult waters that we have to traverse in order to come up with the policy that actually makes good common sense, that will actually save lives and prevent patients in ever-increasing numbers from being on waiting lists for life-saving medications in my state and, indeed, in this country.

In an incredible statement, a Senator from my state who happens to be on the Appropriations Committee says that HIV patients in the State of Colorado are already getting more assistance than they deserve. It is an amazing fact that people who argue for access to care as a human right get labeled lunatics, get labeled as being too personally involved in the care of their communities. This is not acceptable, nor is complacency. Complacency only leads to further prolongation of this problem, and the complacency of physicians will only lead to further problems with access to care, and to increases in the cost of care. It will jeopardize the possibility for future drug discovery, and most importantly, will jeopardize lives. We have already seen patients on waiting lists in two states die while waiting for access to life-saving care, a situation that is frankly unbelievable in this country.

Doctors have to be more involved and cannot just sit on their butts looking for a handout. We are operating in the threshold of the period where we must begin to consider the ethical imperatives and the ethical principles by which we look at this disease and the communities we serve. I believe this very strongly, and I think it is a very positive step for IAPAC and for the other care provider organizations to discuss the fact that physicians and other

healthcare providers have the moral obligation to become involved in this issue. Silence is complacency. Silence is an acquiescence to the status quo, and if you like the status quo then silence is fine.

I happen to think that the 220 or 250 patients in my state who are on waiting lists to receive life-saving medications do not think that the status quo is fine. I would encourage all of us to consider those ethical principles. This is an ethical imperative and silence is not acceptable.

Finally, I would like to tell you about my dear and longest-living patient, Donny. I met Donny in 1995; if you remember the timeline, this was right at the dawn of the PI era. He had progressive multifocal leukoencephalopathy when I first met him. He had a CD4 count of 30 cells/mm³. He had a son who was my daughter's age. In fact, we are the same age. Donny now has a CD4 count of 700 cells/mm³. He is on a drug holiday. He is a success, by the way, of full-dose RTV therapy. He was one of the first patients in the AIDS Clinical Trials Group (ACTG) 315 study, and he is one of the many faces of HIV representing both the successes of therapy and the challenges for all of us, because he has been homeless for most of this time. I used to meet him under a bridge to do his pill counts, to make sure that he was taking his medications. Once again, we talk about public policy, we talk about involvement, we talk about ethical principles, but ultimately it all boils right down to the fact that we are talking about peoples' lives; Donny's life and many other patients' lives, and their families and the communities that are affected by what we do or fail to do. ■

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Silence = complacency

Jenny's HIV diagnosis was confirmed shortly after she presented in his clinic a month ago. He prescribed an antiretroviral regimen based on his firm belief that she would derive both clinical and quality of life benefits. But within days Jenny was one of hundreds of patients on a waiting list to obtain her antiretroviral drugs through Alabama's AIDS Drug Assistance Program (ADAP)—one of more than 1,200 patients on ADAP waiting lists nationwide.

Visit www.iapac.org, to learn about how you may join the International Association of Physicians in AIDS Care (IAPAC) in advocating Jenny's right—indeed, all patients' right—to quality HIV/AIDS care and support.