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Can a Stakeholder Model Work?**

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1. Introduction

As the HIV-AIDS epidemic has spread from wealthy nations to poor ones, especially in sub-Saharan Africa, the pharmaceutical industry has received an extraordinary volume of criticism against the prices and patents of the HIV drugs that can delay the onset of AIDS. HIV drugs are by no means the only topic of criticism in recent years, however. Controversy has extended to prices in the United States, international price disparities among wealthy nations (leading to proposals to import drugs at foreign government-controlled prices; see Wilson 2004), marketing and promotion, and research priorities (Goozner 2004; Angell 2004). Such criticism is hardly new. The 1962 Amendments to the Food, Drug and Cosmetic Act, which greatly expanded FDA regulation and revolutionized drug development, followed upon high-profile Senate hearings highly critical of pharmaceutical research, pricing, and promotion. A 1968 report from the Department of Health, Education and Welfare (predecessor to the Department of Health and Human Services) again set forth in vivid terms a series of criticisms that would seem familiar today (USDHEW 1968; *Journal of Research in Pharmaceutical Economics* 2001).

But international HIV drug prices and patents have probably generated the bitterest criticisms to date, bringing serious threats to the industry's foundations, including intellectual property. This wide-ranging debate has generated proposals to fundamentally transform the pharmaceutical industry. To some extent, these ideas focus on public policy toward patents, prices, government reimbursement, and so on.

A second line of thought, however, suggests that the industry should transform itself to more closely align its practices with wider public interests. The idea (ably propounded by Reisel and Sama 2003 and by Harris, Kennedy, and Lord 2004) is that the industry should abandon its traditional capitalistic model and pursue what might be called a stakeholder model. The stakeholder approach is necessarily plastic as it represents ideals rather than actual practice. Firms would presumably base their business model on the needs of potential consumers with little regard for their ability to pay. Looking well beyond their core business of developing and marketing drugs at a profit, firms would undertake such activities as: (a) ensuring adequate

access to their products (where “access” generally means pricing restraint); (b) abridging or moderating their intellectual property claims including patents; (c) redeploying R&D efforts to address tropical diseases and other diseases endemic in poor nations; and (d) providing financial and in-kind support for measures necessary to ensure that drugs are used where they are needed and are used correctly. In the full blossoming of this approach, the industry would cater to the core interests of all major stakeholders: pharmaceutical firms, patients, health care providers, payers including governments, domestic and international NGOs (where the term non-governmental organization can be expanded to include the World Health Organization and the United Nations). This would involve lower prices, higher expenditures, lower profits (perhaps dramatically lower), and close cooperation with non-governmental organizations and international agencies such as the World Health Organization (WHO) and the United Nations (UN).

Standing in opposition to the stakeholder model is the traditional capitalistic model in which pharmaceutical R&D, marketing, and delivery are driven by the profit motive. To a tolerable approximation, this model can be seen as profit maximization subject to several constraints. These include foreign price controls, price regulations in certain parts of the U.S. government (mainly the V.A. and to a lesser extent, Medicaid), the vagaries of FDA regulation (which covers manufacturing and marketing in addition to new drug approvals), the power of pharmaceutical benefit managers (PBMs) and their clients in managed care, and ultimately, consumer preferences. The pursuit of this traditional model also includes a good measure of lobbying and public relations in order to protect the essentials of pharmaceutical R&D, including patents and other forms of intellectual property, along with a strong measure of freedom in pricing and marketing. It also includes such phenomena as differential pricing (sometimes involving much lower prices in poor nations), free or nominally priced drugs, and public-private partnerships in which pharmaceutical firms cut prices and provide support services. An example is Merck’s “Mectizan Donation Program.” Beginning in 1987, Merck donated its drug Mectizan (ivermectin) to anyone afflicted with river-blindness, for as long as the drug was needed. Most drugs go to Africa, Latin America, and Yemen. The 250 millionth dose was donated in 2002 (Merck 2002).

A word about how we use the term stakeholder is in order. We generally have in mind international agencies such as the WHO and the UN and its affiliates (such as UNAIDS), along

with what are usually referred to as non-governmental organizations, or NGOs. The latter range from wealthy funding organizations (the Bill and Melinda Gates Foundation, for example) to quasi-academic groups such as the International AIDS Society, advocacy groups such as Act-Up, and organizations that provide services as well as advocacy (e.g., Médecins sans Frontières, also known as Doctors Without Borders). Many of these NGOs perform extremely valuable tasks, and their often insightful views merit being heard and attended to. Our concern here, however, is with a system in which these groups and organizations would exercise power over, set policies for, or even allocate resources for the pharmaceutical industry in connection with HIV-AIDS. This stakeholder model or stakeholder approach would extend far beyond traditional modes of regulation and non-governmental advocacy and funding. Our numerous references to the views and criticisms of the various stakeholder groups should be construed as an assessment of their possible effects in a world in which the pharmaceutical industry has adopted a full-scale stakeholder approach to HIV-AIDS. The issue is not whether these groups are well-intended or wise, but what they would have the industry do if the stakeholder model were adopted.

In this paper we assess the stakeholder model for the pharmaceutical industry, with special attention to how this approach might work in connection with the HIV-AIDS epidemic. Before doing so, however, it will be useful to review the basic facts of that epidemic, the drugs that are being used to combat it, drug prices and the circumstances surrounding them, and the prospects for new drugs and other methods necessary to curtail the epidemic.

2. The Worldwide HIV-AIDS Epidemic

The first case of AIDS was identified in June 1981 by scientists at the Centers for Disease Control and Prevention who were intrigued by a series of similar reports from the UCLA Medical Center of rare illnesses among five homosexual males (“Pneumocystis pneumonia -- Los Angeles,” 1981; Gottlieb 2001). Two years later, the retrovirus dubbed HIV (human immunodeficiency virus) was identified as the cause of AIDS; it had been causing isolated infections for at least several years before the 1981 publication.ⁱ Although the latency period between HIV infection and full-blown AIDS can last for years, untreated HIV eventually kills virtually all its victims. In the past 23 years, HIV infection has spread globally (the exact sources remain shrouded in mystery, but human HIV probably jumped from African chimpanzees; see

Stebbing, Gazzard, and Douek 2004). The United Nations agency UNAIDS recently estimated that 38 million people are infected with HIV worldwide. AIDS has claimed more than 20 million lives, including 3 million in 2003 (UNAIDS 2004). Both numbers continue to increase.

Hardest hit by far have been the extremely poor nations of sub-Saharan Africa, where infection rates exceed 35% in Botswana and Swaziland and 20% in South Africa (Halperin and Epstein 2004). Lifespans in that region have been substantially reduced even as they have steadily expanded nearly everywhere else (UNDP 2004). HIV and AIDS have spread to all parts of Asia (as well as Russia and some other parts of the former Soviet Union), causing considerable alarm about the possibility of an African-style epidemic emerging in those far more populous areas (Eberstadt 2002). This has not happened so far, however, and there are reasons to hope that HIV rates in most of Asia, at least, will remain modest (Ruxrungtham, Brown, and Phanuphakp 2004).

HIV is transmitted (although not easily) by unprotected sex (especially male-to-male sex) and (far more easily) by needle-sharing or blood transfusions (Lancet July 3, 2004). Infection is therefore relatively easy to prevent through individual behavior. The fact that the HIV epidemic continues to surge is an indication of the difficulties faced by social marketing in poor nations and regions. The epidemic has largely bypassed non-substance-abusing heterosexuals in advanced economies, and has ebbed and surged among homosexuals in response to behavioral trends (EXPLORE Study Team 2004, Stolte, et al. 2004).

The HIV virus is extremely difficult to control or eradicate once infection has occurred. AIDS itself is amenable only to palliative or delaying treatments, while victims remain exposed to virulent opportunistic infections. In general, the science of the HIV virus is exceptionally difficult to unravel and apply (Cohen 2001, 2002).

3. Worldwide HIV Drug Prices and the Pharmaceutical Industry Crisis

HIV-AIDS Drug Development

The creation of several generations of drugs to treat HIV and AIDS is one of the more remarkable stories in the history of pharmaceuticals. Research began immediately after HIV was identified and continued even as scientists debated the causal role of HIV in AIDS. Government-funded research played a large role (Goozner 2004, ch. 4), but private investment soon surpassed

public research to bring the bulk of HIV drugs to market. The first HIV drug, AZT, was approved in March 1987, only four years after the discovery of HIV (the drug had been studied for other uses; see Goozner 2004, chapter 4), but for several years it was the only FDA-approved HIV drug. Ddi, the first nucleoside reverse transcriptase inhibitor (NRTI) was approved in 1991. In 1995 came the first protease inhibitors, followed by the first nonnucleoside reverse transcriptase inhibitors (NNRTIs). The protease inhibitors inaugurated what has become known as highly active antiretroviral therapy (HAART), the foundation of HIV treatment in all nations. Many of these drugs were created, tested, and brought to market with extraordinary speed given the scientific challenges posed by HIV. The protease inhibitors rapidly and drastically reduced AIDS mortality, enabling many victims to lead fairly complete lives (Palella 1998). By 2004, nearly 30 individual HIV drugs had been approved by the FDA (PhRMA 2003).

HIV-AIDS drugs have brought the industry into controversy primarily because of their prices, but other aspects of these drugs are extremely important. In fact, if HIV drugs were as simple to use as, say the statin class of cholesterol-reducing drugs (such as atorvastatin, sold in the United States as Lipitor), the dispute over pricing would probably have long since been solved with little threat of disruption of the industry. An appreciation of certain aspects of HIV-AIDS drugs is therefore necessary to understanding the controversies these drugs have caused.

Most important are the characteristics of the extraordinary HIV virus itself. Its odd method of reproduction eludes the body's immune system but is extremely error-prone. HIV mutations are routine, not merely as it spreads across a population, but within an individual during treatment (Clavel and Hance 2004). Hence HIV usually survives and eventually thrives when attacked by a single medicine, so that multi-drug treatment is necessary. Drug resistance is a formidable problem, eventually overwhelming all others because all treatments eventually fail (Sande and Ronald 2004, p. 267).

Compliance with therapy is essential. Incomplete, poorly monitored regimens may provide only temporary help for an individual patient while fostering drug resistance in transmittable pathogens, which then create a pool of therapy-resistant patients. The temptation for individual patients to curtail therapy because of costs, side-effects, or other reasons, therefore creates a dangerous externality. These trade-offs raise severe difficulties in both medical administration and public policy, as providing drugs to patients who discontinue or interrupt therapy can wreak harm to the community. The gravity of these problems has captured the

attention of both the medical community and the general public (*Wall Street Journal*, July 8, 2004.) A *Journal of the American Medical Association* editorial by Sande and Ronald (2004, p. 267) noted that meeting treatment goals will require “meticulous, rigorous, compulsive attention to adherence in each patient.” Unfortunately, even compliant therapy can cause problems. A recent study on the use of nevirapine alone to prevent prenatal mother-child transmission concluded that a single dose significantly increased the probability of inducing drug resistance in both mother and child (Jourdain, et al., 2004; Coovadia 2004). When the results were published, the South African government announced that it would switch to a more expensive combination drug. That decision was immediately attacked by the International AIDS Society on the grounds that the higher cost would result in fewer children being protected (*New York Times*, July 14, 2004.)

The science and technology of HIV drugs have had a number of other effects on their use. Some HIV drugs are difficult and expensive to manufacture. Although some drugs compete with each other, the complex nature of HIV infection usually requires the use of several drugs simultaneously. Drug resistance often requires switching among drugs. Opportunistic infections along with endemic illnesses such as TB lead to complex comorbidities in which HIV is not the only condition requiring drug treatment. This can lead to dangerous drug interactions and, again, complex and changing therapies. Unfortunately, simultaneous HIV and TB infections are extremely common. The TB Alliance (2004) estimates that about half of the 30 million HIV infected persons worldwide also have TB.

HIV drugs tend to be powerful, with dangerous side-effects. Determining when to use them, how much to use, and when to interrupt or cease therapy requires using diagnostic tests to assess CD4 cell counts and monitor HIV viral load. This typically requires expert administration and is itself costly. Multi-drug therapy complicates these choices and procedures.

Although a few HIV-positive patients in modern health care systems lead relatively normal lives for years while receiving drug treatment, these drugs are not cures. They are largely palliatives, and for most patients they eventually lose efficacy as the HIV virus mutates.

Pricing

HIV drug pricing is driven by the same forces that govern virtually all drug pricing. Pharmaceuticals are characterized by large costs, lengthy development times, and great financial

risk both while drugs are under development (because even the most promising compounds usually fail in clinical trials) and after they are approved (Spilker 1994). The most extensive research on new drug development costs concluded that on average, each new compound developed in the 1990's cost about \$800 million (estimated for 1997, with costs expected to increase at about 7% annually thereafter) (DiMasi, Hansen, and Grabowski 2003). The researchers also concluded that the returns are so unpredictable that only about three of every ten new drugs generate revenues sufficient to cover the costs of their development (Grabowski, Vernon, and DiMasi 2002).

New drugs are protected by patents. In recent years patents have extended for 20 years from filing, typically leaving perhaps 8 to 15 years of patent protection after clinical trials and the FDA approval process. Manufacturers of patented drugs are free to charge market prices in the United States (albeit with important restrictions for certain government programs including the V.A. and Medicaid). In the U.S., the provisions of the 1984 Hatch-Waxman Act generally permit manufacturers to enter the market with generic versions shortly after patents expire, which quickly drives down prices of major drugs. The Hatch-Waxman Act does not apply to “biologicals,” however, which are drugs that are essentially grown or generated through biological processes rather than being synthesized as relatively simple chemical compounds. Some HIV drugs (Emtriva, for example) are biologicals.

This cost structure generates pricing behavior with two dominant characteristics. First, prices will typically be well above the marginal costs of manufacturing and distribution as manufacturers seek to realize the profits that motivated research investment in the first place. Profit margins are usually restrained, sometimes quite substantially, by competition from similar drugs (Lichtenberg and Philipson 2002). But different HIV drugs treat slightly different conditions or put new mechanisms to work where competing drugs fail. These fairly basic differences presumably inhibit price competition. This is in contrast to such therapeutic categories as the cholesterol-reducing statin drugs or the SSRI antidepressants, where differences among drugs, although often important, are not so great as to forestall competition when manufacturers bargain with buyers. When patents expire, drug prices drop precipitously in the U.S. But because HIV is a relatively new plague, almost no HIV drugs are off-patent. Again, the situation is very different for other major therapeutic categories. The pioneer statin and SSRI brands are already off-patent, with others following rapidly (Express Scripts 2004).

The second basic characteristic of pharmaceutical pricing is that manufacturers have strong incentives to engage in differential pricing (often referred to as price discrimination). Differential pricing increases profits by charging higher prices in markets with greater willingness to pay. This has the benefit of increasing returns to R&D (thus generating more new drugs) while providing drugs to populations that are relatively poor but would gain benefits exceeding marginal costs. If international markets can be kept separate, economic theory suggests that prices will tend to be proportional to per capita GDP (so-called “Ramsay prices,” after the author who first developed this idea at a theoretical level; Danzon and Towse 2003). Differential drug pricing of patented drugs is almost universal. Its greatest benefits can accrue to poor nations. South Africa, for example, has typically seen drugs priced at much lower levels than in Europe and the United States (Reekie 1997).

Differential pricing also invites parallel trade, i.e., trans-shipment of pharmaceuticals from low-price markets to high-price markets. If markets cannot be kept separate, massive parallel trade (which is feasible because shipping and storage costs are typically very low relative to product value) would undermine differential pricing and eliminate its benefits, especially in poor nations, by causing prices to converge at prices prevalent in wealthy nations (cf. Danzon and Towse 2003; Kremer 2002).

These characteristics of pharmaceutical pricing invite governmental controls over price (Frank 2003). Manufacturers are not in a good position to resist price ceilings as long as those ceilings remain comfortably above marginal costs, without regard to the payoffs necessary to induce reasonable levels of R&D. Essentially all economically advanced nations other than the United States control drug prices, employing a wide variety of methods (Danzon and Furukawa 2003; Kanavos 2002). In the United States, controls of one form or another have been implemented for Medicaid and the V.A., and close observers have noted that Medicare may well implement pervasive controls over drug prices in the drug benefit that commences in 2006 (Frank 2003).

Unfortunately, there is no reason to expect price control regimes to take into account the fundamental economics of new drug development. In fact, individual nations have an incentive to use price controls to free-ride on research in other nations, especially the United States, which accounts for roughly half of worldwide revenues (IMS Health *World Review*). This was emphasized by a series of speeches in 2003 by then-FDA Commissioner Mark McClellan

(2003a, 2003b), who is an economist as well as a physician. The resulting disparities between domestic and international prices, including price disparities among wealthy nations, has generated strong political support for the importation of pharmaceuticals from nations with price controls (Wilson 2004).

The political dynamics of HIV drug pricing in poor nations have spilled over to the prices of drugs for other conditions such as heart disease, cancer, and depression, as well as to prices in wealthier nations. Much of this debate was triggered by the World Trade Organization (WTO)'s agreement on intellectual property, known as Trade-Related Aspects of Intellectual Property Rights or TRIPS. The TRIPS agreement has required developing nations to gradually introduce patent protection for various products including pharmaceuticals. A compromise hammered out at the 2001 Doha WTO-TRIPS meetings permits nations to override drug patents in the event of a "public health emergency" (WTO 2001; Kremer 2002).

The TRIPS compromise was intended primarily to encourage the use of generic drugs in poor nations. But the language can apply to all nations, and some advocates argue that the door has been opened for any nation to abridge patent rights by declaring a health care emergency (Kremer 2002). In January 2002, three South Korean groups invoked the TRIPS compromise language in a petition for a compulsory license from the Korean Intellectual Property Office (KIPO) for Glivec (Gleevec in the United States) a Novartis AG drug for chronic myeloid leukemia and other cancers (Nam and Park 2002). South Korean law, like that of most nations, allows for compulsory licenses to be issued to guard against the misuse of patent rights or to protect the public interest. The petition was denied, but the move highlights what is likely to be an increasing trend of undermining intellectual property rights. Unlike the poor African countries for which the Doha mechanism was intended, South Korea has a per capita GDP of over US\$17,000 (2003 dollars at purchasing power parity), roughly 6 times larger than the average per capita GDP in Sub-Saharan Africa.

4. What Has to Be Done to Halt the HIV-AIDS Epidemic?

The prices and availability of drugs have dominated public discussion of the HIV-AIDS epidemic. In fact, the 15th International AIDS conference held in July 2004 in Bangkok, Thailand (sponsored by the International AIDS Society) carried the slogan, "access for all." But

the drugs at the center of so much controversy can only play a relatively limited role in the battle against HIV-AIDS. Progress will be determined largely by factors other than drug prices.

Prevention

Barring unforeseen technological breakthroughs in the next few years, prevention is the only way to halt or reverse the worldwide HIV-AIDS epidemic. This was emphasized in a July 2004 speech by Peter Piot, head of UNAIDS, at the Bangkok conference: “Unless we scale up prevention with the passion and urgency that is being brought to treatment, ‘access for all’ will remain a dream” (*Washington Post*, July 17, 2004). Comparing the epidemic’s pace with the United Nations’ goal of treating 3 million HIV patients by the end of year 2005 (the “3 by 5” campaign), Piot pointed out that at current rates, *eight* million new HIV infections will have occurred in the meantime. Even the most ambitious plans to expand drug therapy cannot keep up with the epidemic. The largest private funding organization, the Gates Foundation, has also argued that “Unless annual HIV incidence falls sharply from its current level of 5 million, treatment programmes will be unable to keep pace with the number of people in need, and will become financially unsustainable” (Gayle and Lange 2004).

Nonetheless, HIV-AIDS remains a very preventable condition even in poor nations. The huge disparities between infection rates in, say, Senegal and those in Botswana or South Africa, are strongly correlated with fundamental differences in sexual practices. In the massively populated Asian nations, HIV has spread very slowly during the two decades or more since it first arrived (again, see Halperin and Epstein 2004, and Ruxrungtham, Brown, and Phanuphakp 2004). Some nations have already realized striking reductions in HIV prevalence: in Uganda, from 21 percent in 1991 to 10 percent in 1998 and 6 percent in 2001 (Low-Beer 2004). Senegal, Zambia, Thailand, and Cambodia have also achieved significant success (Merson 2001).

Infrastructure for Using HIV Drugs

Even if comprehensive drug therapy were possible, grave doubts about its ultimate effects remain. Recent years have seen a rapid drop in HIV drug prices in sub-Saharan Africa by both patent-holders and generic producers, along with relatively free licensing of drugs, the outright abandonment of many drug patents, and the failure of manufacturers to seek patents in most African nations.ⁱⁱ The *Economist* (Nov 27th 2003) noted, “Since 2000, the cost of the drug

cocktail needed to treat AIDS has fallen from \$10,000 per patient annually to \$300.”

But these developments have simply laid bare the high costs of providing HIV therapy even when the drugs themselves are virtually free. In a comment published in *Lancet* on the eve of the Bangkok conference, Kumarasamy (2003) noted that the costs of measuring CD4 cell counts (at \$25) and monitoring viral load (at \$100 per test) exceeds the cost of generic antiretroviral therapy. An estimate of the costs of implementing the United Nations’ “3 by 5” campaign concluded that using low-price generic drugs would cut the cost by less than 20% (Gutierrez, et al. 2004).

The availability of much cheaper HIV drugs also exposed the potential dangers of imperfect drug therapy that could easily occur when the drugs entered widespread use. Complex multi-drug regimens, often dealing with comorbidities, require relatively expensive infrastructures to monitor compliance, efficacy, and drug performance. Moreover, they require diagnostic tests to assess CD4 cell counts in order to start drug treatments neither too early (yielding serious side-effects with little therapeutic gain) nor too late (Sande and Ronald 2004).

The development and rapid approval of fixed-dose combination drugs (FDCs) greatly simplifies administration but increases the risks from side-effects, drug interactions, and individual differences in response to therapy. The specter of noncompliant therapies and a consequent increase in drug-resistant HIV strains raises the alarming possibility that even the best-intended use of current HIV drugs could do more harm than good: “To scale up antiretroviral therapy for HIV without ensuring infrastructure, including trained practitioners, a safe and reliable drug delivery system, and simple but effective models for continuity of care, would be a disaster, leading to ineffective treatment and rapid development of resistance” (Sande and Ronald 2004, p. 267).

Research and Development

What is needed most is a simple, safe and effective HIV vaccine (Cohen 2001 is the indispensable source). Some in the medical research community were once optimistic that the tools that conquered polio would soon be brought to bear against HIV, although few serious researchers endorsed the view of the Health and Human Services Secretary Heckler when she announced in 1984 that an AIDS vaccine would probably be available in two years (Cohen 2001). Creating a vaccine for HIV has proved exceedingly difficult. Some 20 or more vaccines

are currently in trials, including one in a large-scale trial in Thailand partly funded by NIH. But the current consensus in the research community is that the vaccines now in trials represent a very narrow range of mechanisms, that none of the vaccines are likely to prove effective (the one in the Thai trial has already failed in two trials), and that a useful vaccine lies at least a decade in the future (IAVI 2004).

Vaccine development is far from the only R&D challenge in confronting HIV-AIDS. There is much to be done on the current crop of approved drugs. Research goals include preventing mother-child transmission, assessing optimal dosing and drug combinations to forestall resistance, designing simplified and improved combination therapies, better managing side-effects and comorbidities, and creating cheaper diagnostic tests. To a very substantial degree, this research agenda is specific to the resource-limited environment of very poor nations and regions, where simplified treatment regimens are the only feasible option, HIV targets are rapidly evolving, and TB and other comorbidities are endemic (Sande and Ronald 2004). This suggests that the complete abandonment of intellectual property in these nations may be unwise, as patents may be necessary to motivate even the relatively inexpensive research necessary to exploit existing HIV drugs. In fact, the Indian firm Cipla, the most prominent manufacturer of generic HIV drugs for sub-Saharan Africa, recently shocked the international AIDS community by seeking a patent in South Africa for one of its combination drugs (*Wall Street Journal*, July 13).

The new research findings discussed earlier on the prevention of prenatal transmission from mother to child are an example of the research tasks yet to be completed. That research revealed a difficult trade-off: a simple mono-therapy provided reasonably good prevention of transmission but also greatly increased the likelihood that the mother would develop resistance to an essential class of HIV drugs, whereas more expensive combination therapy avoided the resistance problem (at least in the short run) (Jourdain, et al., 2004, Coovadia 2004 and accompanying articles). The discovery of this trade-off caused consternation in the South African government, which has long resisted spending money on sophisticated HIV drugs (*New York Times*, July 14, 2004). The prenatal transmission problem is typical of the trade-offs involved in combination therapy generally, where simplicity and reliability in treatment must often be balanced against side-effects, drug interactions, and efficacy.

Of course, new and better anti-retroviral drugs will always be necessary until we have an

effective vaccine. The basic problem is illustrated by the simple fact that even though we already have almost 30 different HIV drugs, drug treatment often fails or is infeasible in poor nations, and thousands of patients die every year in even the wealthiest nations. The HIV virus' elusiveness and adaptability requires a steady sequence of new drugs. It is perhaps only a matter of time until the HIV variants in Africa and Asia become sufficiently different from those in the United States and Western Europe so that drug development in wealthy nations no longer produces drugs that work equally well in the poverty-stricken regions where the epidemic rages. This is another way in which HIV research is becoming more closely tied to the specific conditions in poor nations and regions.

Finally, there is the seemingly low-tech requirement to create reliable microbiocides, which could prevent transmission through sexual behavior even if these products cannot defeat HIV itself (Coplan, Mitchnick, and Rosenberg 2004).

5. Can the Stakeholder Model Work?

We believe the stakeholder model is fundamentally flawed because it would blunt new drug development while doing little to help solve the problems that motivate the stakeholder model in the first place.

Can Stakeholders Agree, and If So, Would Their Agreements Persist?

We begin by noting that an essential feature of a stakeholder model -- a common set of core interests sufficiently large to form a basis for both industry operations and public policy -- may not exist. As one careful treatment makes clear, the gulf between industry interests and those of NGOs (non-governmental organizations) and other stakeholders is very wide (Reisel and Sama 2003, p. 374, 381). This applies not just to obvious issues like prices but also to the kinds of drugs to develop (so-called "me-too" drugs, i.e., new members of an existing therapeutic class, versus entirely new therapeutic categories), how and where to develop them, how to market them, and how much support to provide for distribution and administration.

The pharmaceutical industry cannot reach explicit or implicit agreements as a group, especially on such sensitive matters as research plans and pricing behavior. Because understandings must encompass research agendas occupying five to fifteen years, entry and exit

may alter the complexion of the industry itself. Even informal enforcement of broad understandings (to pursue a certain line of research, for example) may prove impossible. And if understandings were in fact sufficiently concrete to provide a guide to future behavior, it is hard to imagine how they could withstand antitrust scrutiny.

This is not to say that the pharmaceutical industry and its more responsible critics cannot agree on anything of importance. But even when they do agree, their common interests are unlikely to persist under the pressure of new developments. If manufacturers succeed in developing the products the other stakeholders want -- a malaria vaccine, for example -- they will have created a new situation requiring a new agreement over pricing and distribution. These negotiations are likely to be resolved at price levels that, while providing ample supplies of the new vaccine, would be too low to motivate the next generation of vaccines, and (if such negotiations had been conducted years earlier) would have been too low to have motivated the vaccine now subject to negotiation (Kremer 2002). The fact that reasonable people may disagree on how much profit is needed as an R&D incentive greatly complicates the situation (cf. Reisel and Sama 2003, p. 370, 372; Goozner 2003).

The Stakeholder Model vs. Pharmaceutical R&D

Even if the stakeholders could reach fundamental agreement that would persist in the tumult of politics and marketplace, another and equally fundamental difficulty arises. The consenses envisioned for the stakeholder model generally pertain to pricing, marketing, distribution, and so on, for drugs that already exist. If the stakeholder model is to work, however, it must be forward-looking. Manufacturers must be able to foresee stakeholder agreements and informal understandings years in advance in order to mount the R&D necessary to create the drugs whose prices and availability will one day form the focus of a new round of stakeholder bargaining.

Moreover, this predictable future set of common core interests and mutual understandings would have to provide the profits sufficient to motivate the drug development that stakeholders agree is necessary. This appears to be an insurmountable problem. The nature of a stakeholder agreement five or ten years in the future will depend on a constellation of political and industry forces yet to be fully identified and measured. These include new firms and such inscrutable forces as disease advocacy groups; international developments including the course of

epidemics; changes in medical practice (note the large regional variations in Medicare practice described in Wennberg, Fisher, and Skinner 2002, and striking international variations in, for example, the use of antidepressants, described in *Wall Street Journal*, February 25, 2004); and most important of all, the compensation that governments and organizations will provide for what has been developed. Unfortunately, it is hard to imagine what concrete principles can be expected to apply when challenging drug research is finished (cf. Reisel and Sama 2003 at 381). All this is in addition to the usual uncertainties surrounding R&D such as the robustness of scientific breakthroughs.

Is there any reason to expect the stakeholder approach to overcome these difficulties? Would it promise to yield sufficient foreseeable profits to bring forward the drugs upon which the stakeholders would eventually agree? The best predictor is probably the stakeholder views that have emerged in the past. Those views appear to be relatively unconcerned about R&D incentives. Most stakeholders have long since agreed that the world needs better TB drugs and a good malaria vaccine. But close observers also agree that if those products were developed, the associated intellectual property would not be respected and the firms developing the products could not expect to earn a profit commensurate with the financial risks (again, see Kremer 2002). In fact, some parties who wish to be among the stakeholders in pharmaceutical research envision a world in which the payoffs for developing new drugs would fall far short of recouping R&D investments. Publicly financed investment (which could come in a variety of forms) would become the primary source of new drugs (Hubbard and Love 2004). Michael Kremer and Jeffrey Sachs, recognizing the insecurity of intellectual property for drugs targeted at diseases endemic in developing nations, have proposed the creation of a public fund to guarantee purchase of essential new drugs, such as vaccines and treatments for malaria and TB (Kremer 2002).

The Problem of Costs and Efficiency

The undermining of R&D incentives is perhaps the greatest adverse effect of the stakeholder model for the pharmaceutical industry, but other problems are potentially very important. In a stakeholder-dominated world, parties with no direct financial stake would strongly influence (or even themselves make) decisions ranging from R&D to drug testing, drug manufacturing, and investment in infrastructure. The absence of a market test for these activities invites inefficiency. In the traditional non-stakeholder world, the market penalizes failure even as

it rewards success. The persistent attention to pharmaceutical industry profits tends to obscure the essential role of industry losses in the drug development process. Because the opportunities to spend money on testing potential drugs is for all practical purposes unlimited, a necessary check on spending is the prospect of having to absorb the costs of failure -- as Merck did when four late-stage drug candidates failed in 2003, despite that firm's formidable reputation in pharmaceutical research (*Wall Street Journal*, December 9, 2003).

Equally important are the tasks of manufacturing, distribution, and drug therapy itself. The very mixed record of the WHO and other international organizations on vaccination in poor nations (Mahmoud 2004) suggests that it is unlikely that these organizations will achieve reasonable efficiency in dealing with far more expensive and difficult drug therapies for HIV-AIDS. In an article entitled, "More money, more problems," the *Economist* (July 16, 2004) summed up the situation: "Serious amounts of money are now being made available to deal with AIDS in poor countries. That is good news, but it is bringing its own problems." We note below that African nations with access to large quantities of cheap HIV drugs have often not been able to use them, even in Botswana, perhaps the best-governed sub-Saharan nation.

That assumes that international organizations would undertake most of the work involved in distributing and using pharmaceuticals. But the stakeholder model presumably involves far greater participation by pharmaceutical firms in those arduous and costly tasks. It is hard to know how much firms would be expected to do to ensure access and proper usage, along with propping up or even participating in public health training and enterprises. It is clear, however, that such activities are essentially unlimited in their scope and expense. That raises serious questions about the financial burdens associated with vigorous pursuit of the stakeholder model for the pharmaceutical industry. Without a practical example at hand, it is hard to assess such basic matters as what kind of activities and costs would be associated with the stakeholder model.

6. The Stakeholder Model Applied to HIV-AIDS

The HIV-AIDS crisis is an excellent arena in which to explore at a more practical level how the stakeholder model would work, and to illustrate the fundamental difficulties in such an approach.

Where Is the Consensus?

The pharmaceutical industry has continued to develop new HIV drugs as older ones encounter the inevitable problem of drug-resistant HIV strains. PhRMA, the industry trade organization, lists approximately 80 HIV drugs and vaccines in development (PhRMA 2003). This is despite the fact that a decade and more of criticism, along with a shift in the locus of the epidemic from wealthy to very poor regions, has undoubtedly deterred some firms from entering a market characterized by indifferent returns and difficult public relations. The present authors and others have frequently been informed privately that large firms have refrained from entering the HIV-AIDS market and indeed, feel a certain sense of relief that they had not done so earlier. Bate (2003) documented that 27 percent fewer companies were working on ARV research in 2003 than in 1997, with fewer new compounds in the development phase.

Prices have also plunged in the past several years and patents in sub-Saharan Africa are essentially abandoned or unenforced (as discussed below). Nonetheless, intense criticism of the industry continued at the July 2004 Bangkok conference, where the Pfizer CEO and the chief of the U.S. AIDS program were booed by the audience when they prepared to speak (*Atlanta Journal-Constitution*, July 14, 2004). Much of the criticism focused on the fact that the United States, which is by far the largest funder of HIV-AIDS programs in sub-Saharan Africa, has waited for FDA approval of new combination generic drug formulations rather than immediately purchasing generic brands already approved by the WHO using a less thorough scientific assessment (Bate and Tren 2004). Both activists and mainstream international HIV-AIDS organizations have essentially rejected the idea that either the U.S. or other organizations should purchase branded drugs rather than the cheapest available generics. This kind of thinking, which essentially eliminates industry profits from serving the needs of poor nations, leaves no room for a consensus that includes the industry itself.

Other signs also suggests that stakeholder consenses will not easily be forged. The industry has engaged in a number of initiatives to support public health activities including AIDS-related operations. Merck, for example, has entered into arrangements with four African countries including Botswana, where Merck and the Bill and Melinda Gates Foundation (Gates Foundation) have each given \$US 50 million over 5 years to support and enhance the government's public health program. Pfizer has funded the construction of an HIV-AIDS clinic and research and training institute at Makerere University Medical School, Kampala. That

operation is being run by the Academic Alliance for AIDS Care & Prevention, where US experts are training doctors, nurses, and others in treating infectious diseases. It is also training PhDs and building up a center of excellence. There seems little reason, however, to think that these and other activities have been given significant weight by other stakeholders.

An example is the fate of the Accelerated Access Initiative (AAI), a public-private partnership involving several pharmaceutical firms and the Joint United Nations Program on HIV/AIDS (UNAIDS), that was launched in May 2000.ⁱⁱⁱ AAI sought to improve HIV-AIDS prevention, treatment, and care. Success has been mixed, as it involves drug industry involvement in activities for which they have no particular expertise or comparative advantage. Drug activists, however, have dismissed the AAI as a public relations exercise by drug companies and have accused them of using the initiative to discourage developing countries from using cheap generic drugs in order to maintain a larger share of the market for their patented versions (despite the minimal role of patent; see Act-Up Paris 2002).

One might think that once a manufacturer has decided to provide an essential drug at very low prices, or even for free, constructing a stakeholder consensus on whether to use the drug and how to use it would be relatively straight-forward. Unfortunately, this is not necessarily true. An illuminating example is the tortured deliberations and false starts that accompanied the introduction of a superior combination malaria drug combination in Kenya in the late 1990s (Shretta, et al. 2001). The most difficult issues in that episode -- drug resistance, the impact on the overall health system, infrastructure requirements, and so on -- are familiar themes, but the difficulties are far greater when one moves from malaria to HIV-AIDS drug treatment.

These developments, ranging from small-scale activities to massive changes in prices and intellectual property protections, suggest that a broad consensus or understanding is unlikely to emerge with sufficient force and stability to support a stakeholder approach that includes a reasonable role for the pharmaceutical industry in HIV-AIDS. Rather, a consensus would leave pharmaceutical firms with little role beyond developing new drugs (if they can) and then essentially giving them away.

HIV Drug Patents in Africa

With the possible exception of drug prices, no topic in worldwide HIV-AIDS has been more contentious than patents, especially in sub-Saharan Africa. Much of this was triggered by a

1998 lawsuit brought by the industry against the South African government when it sought to authorize use of generic versions of patented drugs. The furor over that litigation, which was settled in 2001 largely on the government's terms (*Wall Street Journal*, April 18, 2001), tended to obscure two essential points.

One is that the industry's primary motive in the patent litigation was apparently simply to maintain its intellectual property rights, not so much with the idea of propping up prices but rather with the objective of maintaining control over trans-shipment from low-price to high-price countries (PhRMA April 18, 2001). The second point is that on the whole, HIV drug patent rights have been indifferently sought or awarded, and have had negligible effect. With a few exceptions, HIV drug patents have been very rare in sub-Saharan Africa. In their census of HIV patents in that region, Attaran and Gillespie-White (2001) found that most nations did not respect patents at all, that most HIV drugs were not patented where patents were offered, and that the state of patenting bore little relationship to the actual use of HIV drugs. Regardless of the existence of patents, several drug developers have offered their drugs at discounted prices or for free to developing nations (again, see *Economist*, Nov 27th 2003, and TREAT Asia 2004). In addition, some companies, such as GSK and Bristol Myers Squibb have entered into voluntary license agreements allowing generic drug companies to produce copies of their patented drugs (*Wall Street Journal*, October 8, 2001).

R&D Incentives (Including in Poor Nations)

We have described the wide range of R&D activities necessary to restrain or curtail the HIV-AIDS epidemic. We also noted that much of this research is (or would be, if it comes to pass) devoted to matters that are relevant mainly to very poor regions such as sub-Saharan Africa. Thus R&D incentives are an essential factor in assessing a stakeholder approach to HIV-AIDS.

In a sense, a stakeholder model is likely to diminish R&D incentives simply by making the pharmaceutical industry a more costly enterprise as manufacturers meet the expanded requirements of diverse groups and organizations. But there are also two specific ways in which the stakeholder approach could undermine R&D.

One pertains to the question of what prices and profits can be realized after firms develop innovative drugs. Of course, economic demand from the populations of sub-Saharan Africa is

extremely small (although it would escalate if and when these nations are governed sufficiently well to permit economic development to catch up with emerging economies such as India and China). On the other hand, there is strong potential demand from the organizations funded by the wealthy nations and individuals of the west. These organizations range from the U.S. government to WHO, the World Bank, and the Gates Foundation. They could provide the potential payoffs that would motivate R&D aimed at the HIV-AIDS needs of even the poorest nations. Unfortunately, there is little likelihood that a stakeholder consensus would involve such incentives. The unrelenting and nearly unanimous plea for all international organizations, including U.S. government agencies, to purchase either generics or branded drugs at generic prices largely rules out the possibility that a stakeholder model would generate reasonable R&D incentives.

A second issue relates to R&D operations in sub-Saharan Africa itself. South Africa was one of few African nations ever to have had a large and profitable research-based pharmaceutical sector. The past decade has seen a gradual decline in South Africa of pharmaceutical manufacturing (and therefore expertise and technology transfer), with approximately 25 drug manufacturers closing their plants. To some extent this reflects the wave of consolidations in the industry worldwide, but the growth and entrenchment of anti-industry attitudes and laws in South Africa has surely contributed to this decline. This trend, which as we have seen is buttressed by most putative stakeholder interests, seems likely to discourage the rebirth and growth of an indigenous pharmaceutical research industry. Also relevant are events in India, whose longstanding inward-looking pharmaceutical industry has become prominent in the world generic drug market. The Indian pharmaceutical industry has also begun to move aggressively into original research, utilizing that vast nation's reservoir of technical talent, but it is perfectly clear that this development relies upon the establishment of patent rights and the prospect of profits rather than a new stakeholder consensus (*Wall Street Journal*, November 13, 2003).

Bottlenecks and Drug Access

If international agencies and sub-Saharan African governments had been ready to use HIV treatments when they became affordable, we would have seen a swift expansion in HAART for the several million HIV victims whose CD4 counts indicated they were ready for drug therapy. A number of surveys have found that this did not occur after drug prices plummeted and

generic manufacturers entered. The reasons are several.

In some cases national governments simply refused to pursue HAART. Perhaps the most remarkable example occurred in South Africa, where the health minister announced to a shocked crowd of AIDS activists in 2001 that she did not intend to distribute the generic drugs that had just become available after settling the industry litigation over drug patents (*New York Times*, June 28, 2001). One reason is that both South African President Mbeki and Health Minister Manto Tshabalala Msimang publicly doubted that HIV was the cause of AIDS, and believed that antiretroviral therapy would do more harm than good. The Minister recently affirmed a long-standing position opposed to widespread use of antiretrovirals to prevent prenatal HIV transmission, recommending breast-feeding instead (*New York Times*, December 20, 2001; *Business Day*, 12 July 2004). Earlier, the Minister had stated that she would not support using ARV drugs in government-run hospitals until monitoring and care matched the standards of Western European hospitals (*New York Times*, June 28, 2001).

In other nations, the problem has not been hostility toward HAART but an apparent inability to take advantage of drugs (and supporting funds) when they became available. The evidence from Botswana is that political will and bureaucratic competence is probably more important in tackling HIV-AIDS than cash contributions from the pharmaceutical industry or other sources (Tren 2003).

This is typical of events in sub-Saharan Africa in the past few years. Despite the efforts of pharmaceutical firms and international agencies, treatment rates in Africa continue to be extremely low: less than 7 percent of persons for whom ARV treatment is indicated (Gayle and Lange 2004). This is despite huge increases in spending along with the rapid decline in drug prices. The largest single international effort, the Global Fund to Fight AIDS, Tuberculosis and Malaria, has been greatly delayed in awarding and disbursing grants because of the inability of recipient nations to meet the Fund's standards for performance-based disbursement (Brugha, et al. 2004).

This is not to say, of course, that these nations should simply plunge ahead with using whatever drugs are available. That would do more harm than good by accelerating drug resistance while helping very few victims. These nations face very difficult choices when deciding on mass HIV drug treatment, and these choices involve substantial commitments including getting trained physicians into the field (Kumrasamy 2004). Rather, the point is that

drug prices and access are not the main obstacles to effective treatment.

New Tasks, New Costs

Although the elements of the stakeholder model are anything but clear, one of those elements is probably that pharmaceutical firms will do much more than just develop, manufacture, and market drugs. They should also serve as sources of expertise, funding, and perhaps even personnel, for the larger tasks of delivering and administering drug therapy along with associated activities such as diagnostics and monitoring.

This raises two difficulties. One is cost. The relentless push for generic drugs, which promises to be part of any consensus approach to HIV-AIDS in poor nations, effectively removes industry profits from this market. Yet the extra costs of making HAART work in practice are likely to be very large, as evidenced by the slow pace of HAART in places where considerable sums are already being spent. There seems little reason to saddle pharmaceutical firms with costs that bear no relationship with the industry's resources. In fact, one has to ask how the industry could supply the needed sums, given the presumed lack of profits from HIV drugs. The answer would be, profits from drug sales in other regions and for non-HIV products. This reasoning suggests that as a stakeholder model becomes more likely, the financial incentives for firms to exit from the HIV-AIDS market grow stronger.

The other difficulty lies in the notion of comparative advantage. One of the two essential elements in winning the battle against HIV-AIDS -- an effective vaccine or an outright drug cure -- can be supplied only by R&D that will be funded primarily in the private sector. (The other element, good governance, is discussed next.) Although considerable public and non-profit resources are being spent on vaccine development, the historical record of similar work on TB and malaria suggests little likelihood that the solution will emerge from that sector. R&D is the supreme comparative advantage of the private pharmaceutical sector.

On the other hand, to hold the industry responsible for efficient distribution and use of drugs is to ask the industry to undertake activities in which it has little comparative advantage. In developed nations, the industry does not perform the bulk of such routine activities as storage and distribution, leaving much of that to specialist wholesalers. Pharmaceutical firms are traditionally rather distant from the actual use of all but a few specialty drugs. In the far more difficult circumstances of treating HIV-AIDS in very poor nations, industry expertise is even less

relevant. Given such needs as cold storage for many HIV drugs, it would probably make more sense to involve large fresh grocery chains such as Tesco, or rely upon agencies with a good track record, such as International Healthcare Distributors (IHD) in South Africa. At any rate, there is little doubt that specialized expertise is needed. We have noted that international agencies have done a surprisingly poor job of distributing other, simpler products, such as antibiotics and vaccines, that also require special handling (Mahmoud 2004).

Events in Botswana illustrate some of these points. Botswana has the highest rate of HIV infection in the world, estimated at slightly more than 1/3 of the adult population. We noted earlier that the pharmaceutical firm Merck and the Gates Foundation have offered tens of millions of dollars for HIV-AIDS work in that nation. To date, the efforts in Botswana have been highly successful, although less successful than the country's leadership had hoped. By June 2004, a large number of HIV-AIDS clinics had been built and around 15,000 Botswanans were receiving treatment. (This was well under the government's goal of 60,000, presumably because of a combination of stigmatization, ignorance, and inaccurate estimates of the HIV-positive population.) Despite these successes, most of the government's AIDS budget remains unspent (Attaran, personal communication). Despite Merck's cash and in-kind contributions, Botswana wisely uses many non-Merck drugs in order to employ several different triple therapies. The success of this enterprise clearly depends not on pharmaceutical expertise but on organizational skills, political will, and continued funding from any available source.

The Governance Problem

That the bulk of sub-Saharan African nations are poorly governed is hardly a matter of dispute. The poverty that both fosters the spread of HIV-AIDS and hinders its treatment is widely thought to be an inevitable consequence of governance that often barely reaches rudimentary levels.

Several signs suggest that dramatic progress against HIV-AIDS may have to await improvements in governance. On the whole, the nations that have seen striking improvements in how they are governed (Uganda, Botswana) have also made the most progress in the battle against HIV-AIDS.

Nonetheless, serious governance problems remain even in South Africa, one of the most enlightened sub-Saharan nations. Home to the largest HIV-positive population in the world,

South Africa has been unable to spend its HIV-AIDS budget. Quite apart from the public doubts about HIV therapy expressed by South Africa's President and Minister of Health, the provinces frequently roll over their AIDS budget to subsequent financial years because they do not have the capacity to spend it (Johannesburg *Sunday Times*). On the other hand, the overall health infrastructure, including higher level medical staff and educational facilities, remain severely underfunded as many of the best personnel migrate to wealthier nations. This is unfortunate because strong intellectual capabilities are needed to make the difficult choices necessary to propagate reasonable and efficient practices in treating HIV-AIDS. (In the meantime, South Africa recently chose to spend \$5.73 billion on armaments despite an apparent lack of foreign threats. See *The Guardian*, December 17, 2002.)

7. Conclusions: The Dangers of Abandoning the Traditional Profit-Motivated Model

It is natural that the worldwide HIV-AIDS epidemic would focus attention, much of it critical, on the pharmaceutical industry. Its unique cost structure ensures both large profit margins and striking international price disparities. Its prices and profits are supported by the slender thread of government-granted patents, which can be removed as easily as they are granted, absent international agreements prohibiting patent abridgment. The fact that HIV-AIDS migrated rapidly and relentlessly from wealthy nations to the very poorest regions brought all these factors into sharp relief. The fact that the greatest beneficiaries of future research breakthroughs would be the world's poorest people dictates that the preservation of R&D incentives will be a delicate task in public policy.

In a fundamental sense, much of the criticism of drug pricing and related matters in treating HIV-AIDS in poor nations is misplaced. A rapid drop in prices, accompanied by a near-abandonment of intellectual property and the widespread availability of inexpensive generic drugs, has revealed that stumbling blocks in progress against HIV-AIDS in sub-Saharan Africa are not drug prices or patents. Rather, the barriers are inadequate health care infrastructures, an inability to administer drug therapy when it is needed and to avoid inappropriate drug therapy, the threat and reality of drug-resistant HIV strains, opposition to reasonable HIV therapy by governments, and severe administrative bottlenecks that have nothing to do with drug pricing or availability. Also clear is that much R&D remains to be done in how to use the drugs that are

now available, and in the development of new drugs, especially vaccines, if the HIV-AIDS epidemic is to be curtailed before it runs its natural and tragic course.

Many critics of the industry's behavior in connection with HIV-AIDS have nonetheless arrived at the simplest of solutions: taking away patent rights, requesting cost-based drug supplies or free licensing to generic manufacturers. At the same time, however, we have also seen a firestorm of criticism of the pharmaceutical industry in a much broader context, focusing on price disparities among wealthy nations and on the high costs in developed economies of both R&D and the products generated by R&D. The upshot has been proposals for a new approach to the drug industry, involving not only changes in public policy but the remarkable idea that the industry itself should adopt what might be called a stakeholder model to replace the traditional capitalist, profit-driven stockholder model.

Although the stakeholder model is hardly a well-defined one, serious problems are raised by what seem to be its essential elements. Among these are an inability to forge a lasting and predictable consensus on such basic matters as R&D and pricing, unnecessary costs and inefficiencies, and a near-certain undermining of R&D incentives.

These difficulties gain force and concreteness when the stakeholder model is arrayed against the specifics of the HIV-AIDS crisis in what are often referred to as the "resource-limited" economies of sub-Saharan Africa. It is hard to imagine what the terms of a stakeholder approach might be, how that approach could help solve the problems facing those nations, or how it could help generate the new medical technology -- especially vaccines -- that are desperately needed and are least likely to emerge from the government or non-profit sectors.

One potential and tragic cost of a new regime in which some sort of stakeholder model prevails is that the world HIV-AIDS market could become completely segmented. Pharmaceutical firms would develop drugs for the HIV variants found in wealthy nations, providing progressively less help to the poorest nations as their respective HIV populations steadily diverge. We would arrive at a situation parallel to that prevailing for malaria and TB, where the drugs sufficient to treat the few victims in wealthy nations are of limited use in the countries where victims number in the millions and where no new TB drugs have been introduced in decades. The stakeholders will have been left with very little to show for abandoning the traditional drug development model.

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i. The tangled history of the discovery of the HIV virus, the enduring controversy over priority, and the intense debate over whether HIV was indeed the primary cause of AIDS, is recounted in Jon Cohen's superb 2001 monograph. Gottlieb 2001 provides a convenient synopsis of this history.

ii. HIV drug prices are tracked in *Economist*, Nov 27th 2003, and TREAT Asia 2004. On the near-absence of HIV drug patents in Africa, see Attaran and Gillespie-White 2001, whose results are discussed below.

iii. The companies involved are Boehringer-Ingelheim, Bristol-Myers Squibb, GSK, Merck, and Hoffman-La Roche.

Executive Summary

The worldwide HIV-AIDS epidemic has generated intense criticism of pharmaceutical drug prices, a natural consequence of the industry's unique cost structure. A number of persons have proposed that the industry adopt what might be called a stakeholder model in place of the traditional profit-driven model. But the rapid drop in HIV drug prices, combined with generic entry and *de facto* abandonment of patent rights, has revealed the extremely limited role played by drug prices and access in the face of fundamental problems in infrastructure, prevention, and other essential elements in battling HIV-AIDS. Adoption of a stakeholder approach is likely to undermine essential R&D while doing little to curtail the HIV-AIDS epidemic.