

Pharmaceuticals and the Worldwide HIV Epidemic: Can a Stakeholder Model Work?

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The worldwide HIV/AIDS epidemic has generated intense criticism of pharmaceutical drug prices, a natural consequence of the industry's unique cost structure. Many people have proposed that the industry adopt what might be called a stakeholder model in place of the traditional profit-driven model. However, the rapid drop in HIV drug prices, combined with generic entry and de facto abandonment of patent rights, has revealed the extremely limited role of 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 research and development while doing little to curtail the HIV/AIDS epidemic.

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 of the prices and patents of the HIV drugs that can delay the onset of AIDS. However, HIV drugs are by no means the only topic of criticism in recent years. Controversy has extended to prices in the United States, international price disparities among wealthy nations (which has led to proposals to import drugs at foreign government-controlled prices; see Wilson 2004), marketing and promotion, and research priorities (Angell 2004; Goozner 2004). Such criticism is hardly new. The 1962 amendments to the Food, Drug and Cosmetic Act, which greatly expanded Food and Drug Administration (FDA) regulation and revolutionized drug development, followed on high-profile Senate hearings that were highly critical of pharmaceutical research, pricing, and promotion. A report from the U.S. Department of Health, Education, and Welfare (1968; predecessor to the Department of Health and Human Services) listed, in vivid terms, a series of criticisms that would sound familiar today (see also *Journal of Research in Pharmaceutical Economics* 2001).

However, international HIV drug prices and patents have probably generated the most bitter 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.

Another line of thought suggests that the industry should transform itself to align its practices more closely with wider public interests. The idea (see Kennedy, Harris, and Lord 2004; Reisel and Sama 2003) is that the industry

should abandon its traditional capitalistic model and pursue what might be called a stakeholder model. The stakeholder approach is not clearly defined because it represents certain parties' ideals rather than actual practice. Firms would presumably begin with the needs of potential consumers, regardless of their ability to pay. Moving well beyond their core business of developing and marketing drugs at a profit, firms would undertake such activities as (1) ensuring adequate access to their products (where "access" generally means price restraint); (2) abridging or moderating their intellectual property claims, including patents; (3) redeploying research and development (R&D) efforts to address tropical diseases and other diseases endemic in poor nations; and (4) providing financial and in-kind support for measures that are necessary to ensure that drugs are used where they are needed and 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, and payers including governments and domestic and international nongovernmental organizations (NGOs). This would involve lower prices, higher expenditures, lower profits (perhaps dramatically), and close cooperation with NGOs and international agencies, such as the World Health Organization (WHO) and the United Nations (UN).

In contrast 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 viewed as profit maximization that is subject to several constraints. Such constraints include foreign price controls, price regulations in certain parts of the U.S. government (mainly the Veteran's Affairs [VA] 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 and their clients in managed care, and, ultimately, consumer preferences. The pursuit of this traditional model also includes lobbying and public relations to protect the essentials of pharmaceutical R&D, including patents and other forms of intellectual property, along with freedom in pricing and marketing. It also

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includes 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." From 1987, Merck has donated its drug Mectizan (ivermectin) to anyone afflicted with river-blindness, for as long as the drug is needed. Most drugs go to Africa, Latin America, and Yemen. In 2002, the 250 millionth dose was donated (Merck 2002).

In general, when we use the term "stakeholder," we have in mind international agencies such as the WHO and the UN and its affiliates (including UNAIDS), along with NGOs. The latter range from wealthy funding organizations (e.g., the Bill and Melinda Gates Foundation) to quasi-academic groups such as the International AIDS Society, advocacy groups such as Act-Up, and organizations that provide services and advocacy (e.g., *Médecines sans Frontiers*, 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. However, our concern here 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 would extend beyond traditional modes of regulation and non-governmental advocacy and funding. Our many 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-intentioned or wise, but what they would have the industry do if the stakeholder model were adopted.

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

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 University of California, Los Angeles, Medical Center of rare illnesses among five homosexual men (Gottlieb 2001; *Mortality and Morbidity Weekly Report* 1981). 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.¹ Although the latency period between HIV infection and full-blown AIDS can last for many years, untreated HIV eventually kills all its victims. In the past 23

years, HIV infection has spread globally (the exact sources remain shrouded in mystery, but human HIV probably derived from African chimpanzees; see Stebbing, Gazzard, and Douek 2004). The agency UNAIDS recently estimated that 38 million people are infected with HIV worldwide. AIDS has claimed more than 20 million deaths, 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). Life spans in that region have been substantially reduced even as they have steadily increased nearly everywhere else (United Nations Development Programme 2004). Both HIV and AIDS have spread to all parts of Asia, as well as Russia and some other parts of the former Soviet Union, giving rise to considerable alarm that an African-style epidemic might emerge in far more populous areas (Eberstadt 2002). This has not happened to date, 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, though not easily, by unprotected sex and far more easily by needle sharing or blood transfusions (*Lancet* 2004). Therefore, infection is relatively easy to prevent through individual behavior. That the HIV epidemic continues to surge is an indication of the difficulties that social marketing in poor nations and regions faces. The epidemic has largely bypassed nonsubstance-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).

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

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 a remarkable story 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, Ch. 4), but for several years it was the only FDA-approved HIV drug. Ddi, the first nucleoside reverse transcriptase inhibitor, was approved in 1991. In 1995 came the first protease inhibitors, followed by the first nonnucleoside reverse transcriptase inhibitors. 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

¹Cohen (2001) recounts the tangled history of HIV's discovery, the enduring controversy with respect to priority, and the intense debate about whether HIV was indeed the primary cause of AIDS. Gottlieb (2001) provides a convenient synopsis of this history.

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 et al. 1998). By 2004, the FDA had approved nearly 30 individual HIV drugs (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. Indeed, if HIV drugs were as simple to use as, for example, the statin class of cholesterol-reducing drugs (e.g., 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 necessary to understand the controversies these drugs have caused.

Most important are the characteristics of HIV 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 a patient during treatment (Clavel and Hance 2004). Thus, HIV usually survives and eventually thrives when attacked by a single medicine, so that multidrug 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 creates a dangerous externality. These trade-offs raise difficulties in both medical administration and public policy, because provision of drugs to patients who discontinue or interrupt therapy can harm the community. The gravity of these problems has captured the attention of both the medical community and the general public (Altman 2004.) In their editorial, Sande and Ronald (2004, p. 267) note that meeting treatment goals requires "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; see also Coovadia 2004). When the results were published, the South African government announced that it would switch to a more expensive combination drug. The International AIDS Society immediately attacked that decision on the grounds that the higher cost would result in fewer children being protected (LaFraniere 200).

The science and technology of HIV drugs has had other effects on their use. Some HIV drugs are difficult and expensive to manufacture. Although some drugs compete with one another, the multifaceted nature of HIV infection usually requires the use of several drugs simultaneously. Drug resistance often requires switching drugs. Opportunistic infections and endemic illnesses such as tuberculosis (TB) lead to complex comorbidities in which HIV is not the only condition requiring drug treatment. This can lead to

dangerous drug interactions as well as complex and changing therapies. Unfortunately, simultaneous HIV and TB infections are extremely common. The TB Alliance (2004) estimates that approximately half of the 30 million HIV-infected people 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 the use of diagnostic tests to assess CD4 cell counts and monitor HIV viral load. This typically requires expert administration and is itself costly. Multidrug 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 HIV 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). In the most extensive research on new drug development costs, DiMasi, Hansen, and Grabowski (2003) conclude that, on average, each new compound developed in the 1990s cost approximately \$800 million (estimated for 1997, with costs expected to increase at almost 7% annually thereafter). The researchers also conclude that the returns are so unpredictable that only about three of every ten new drugs generate sufficient revenues 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 VA and Medicaid. In the United States, 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. However, the Hatch-Waxman Act does not apply to "biologicals," which are drugs that are essentially grown or generated through biological processes rather than synthesized as relatively simple chemical compounds. Some HIV drugs (e.g., Emtriva) 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 initially motivated research investment. Profit margins are usually restrained, sometimes substantially, by competition from similar drugs (Lichtenberg and Philipson 2002). However, different HIV drugs treat slightly different conditions or put new mechanisms to work when competing drugs fail. These fairly basic differences presumably inhibit price competition. This is in contrast to therapeutic categories such as the

cholesterol-reducing statin drugs or the selective serotonin reuptake inhibitor antidepressants, in which case differences among drugs, though often important, are not so great as to forestall competition when manufacturers bargain with buyers. When patents expire, drug prices drop precipitously in the United States, but because HIV is a relatively new plague, almost no HIV drugs are off-patent. Again, the situation is different for other major therapy categories. The pioneer statin and selective serotonin reuptake inhibitor brands are already off-patent, with others to follow rapidly (Express Scripts 2004).

The second characteristic of pharmaceutical pricing is that manufacturers have strong incentives to engage in differential pricing (which is 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 that would gain benefits that exceed marginal costs. If international markets can be separated, economic theory suggests that prices will tend to be proportional to per capita gross domestic product (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. For example, South Africa has typically received drug prices at much lower levels than those in Europe and the United States (Reekie 1997).

Differential pricing also invites parallel trade, that is, trans-shipment of pharmaceuticals from low-price markets to high-price markets. If markets cannot be separated, massive parallel trade, which is feasible because shipping and storage costs are typically 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 (see 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 the ceilings remain comfortably above marginal costs, without regard to the payoffs necessary to induce reasonable R&D levels. 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 different forms have been implemented for Medicaid and the VA, 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 controls regimes to take into account the fundamental economics of new drug development. 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 2003). This was emphasized by a series of speeches in 2003 by then-FDA Commissioner Mark McClellan (2003a, b), who is both an economist and a physician. The resultant disparities between domestic and international prices, including price

disparities among wealthy nations, have generated strong political support for the importation of pharmaceuticals from nations with price controls (Wilson 2004).

The political dynamics of HIV pricing in poor nations have spilled over to other pharmaceuticals and wealthier nations, as Kennedy, Harris, and Lord (2004) emphasize. In poor nations, the drug price debate has extended to patented drugs for other illnesses such as coronary heart disease, cancer, and depression. Much of this debate was triggered by the WTO's agreement on intellectual property, known as trade-related aspects of intellectual property rights (TRIPS). The TRIPS agreement requires developing nations to introduce patent protection gradually 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 (Kremer 2002; WTO 2001).

The TRIPS compromise on pharmaceutical patents was intended primarily to encourage the use of generic drugs in poor nation, 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 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, as that of most nations, allows 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 emphasizes what is likely 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 more than US\$17,000 (2003 dollars at purchasing power parity), which is roughly six times larger than the average per capita GDP in sub-Saharan Africa.

What Must Be Done to Halt the HIV/AIDS Epidemic?

The prices and availability of drugs have dominated public discussion of the HIV/AIDS epidemic. The 15th International AIDS conference, sponsored by the International AIDS Society and held in July 2004 in Bangkok, Thailand, carried the slogan, "access for all." However, the drugs at the center of so much controversy can play only 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" (Nakashima and Brown 2004, p. A13). Comparing the epidemic's pace with the UN's goal of treating three million HIV patients by the

end of 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 expansive plans to expand drug therapy cannot keep up with the epidemic. The largest private funding organization, the Gates Foundation, has also argued that “[u]nless 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, p. 6).

Nonetheless, HIV/AIDS remains a preventable condition even in poor nations. The huge disparities in infection rates between, for example, Senegal and Botswana or South Africa are strongly correlated with fundamental differences in sexual practices. In the massively populated Asian nations, HIV has spread slowly during the two decades or more in which it has been indigenous (see Halperin and Epstein 2004; Ruxrungtham, Brown, and Phanuphakp 2004). Some nations already have realized striking reductions in HIV prevalence: in Uganda, from 21% in 1991 to 10% in 1998 and 6% 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 witnessed a rapid drop in HIV drug prices in sub-Saharan Africa by both patent holders and generic producers, in addition to relatively free drug licensing, the outright abandonment of many drug patents, and the failure of manufacturers to seek patents in most African nations.² *The Economist* (2003, pp. 77–79) noted, “Since 2000, the cost of the drug cocktail needed to treat AIDS has fallen from \$10,000 per patient annually to \$300.”

However, these developments have simply exposed 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) exceed the cost of generic antiretroviral therapy. An estimate of the costs of implementing the UN’s “3 by 5” campaign shows 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 multidrug regimens, which often involve 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 minimal therapeutic gain) nor too late (Sande and Ronald 2004).

The development and rapid approval of fixed-dose combination drugs greatly simplifies administration but increases the risks from side effects, drug interactions, and individual differences in response to therapy. The prospect of noncompliant therapies and a consequent increase in drug-resistant HIV strains raise 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).

R&D

What is needed most is a simple, safe, and effective HIV vaccine (Cohen 2001). Some researchers in the medical community were once optimistic that the tools that conquered polio would soon be brought to bear against HIV, though few serious researchers endorsed the view of the Health and Human Services Secretary Heckler when, in 1984, she announced that an AIDS vaccine would probably be available in two years (Cohen 2001). Creation of 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 that is partly funded by the National Institute of Health. The current consensus in the research community is that the vaccines now in trials represent a narrow range of mechanisms, that none of the vaccines are likely to prove effective (the one in the Thai research has already failed in two trials), and that a useful vaccine lies at least a decade in the future (International AIDS Vaccine Initiative 2004).

Vaccine development is far from the only R&D task in dealing with HIV/AIDS. There is much to be done on the current crop of approved drugs. Research goals include preventing mother–child transmission, assessing optimal dosage 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 substantial degree, this research agenda is specific to the resource-limited environment of poor nations and regions, in which 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 is unwise, because patents may be necessary to motivate even the relatively inexpensive research necessary to exploit existing HIV drugs. 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 (*The Wall Street Journal* 2004).

The new research findings we discussed previously on the prevention of prenatal transmission from mother to child are an example of the research tasks that are yet to be completed. That research revealed a difficult trade-off: A simple monotherapy provided reasonably good prevention of transmission but also greatly increased the likelihood that the mother would develop resistance to an essential class of

²HIV drug prices are tracked in *The Economist* (2003) and TREAT Asia (2004). On the near-absence of HIV drug patents in Africa, see the work of Attaran and Gillespie-White (2001), whose results we discuss subsequently.

HIV drugs, whereas more expensive combination therapy avoided the resistance problem, at least in the short run (Coovadia 2004; Jourdain et al. 2004). The discovery of this trade-off caused consternation in the South African government, which has long resisted spending money on sophisticated HIV drugs (LaFraniere 2004). The prenatal transmission problem is typical of the trade-offs involved in combination therapy in general, for which simplicity and reliability in treatment often must be balanced with side effects, drug interactions, and efficacy.

New and better antiretroviral drugs will be necessary until an effective vaccine is available. The basic problem is illustrated simply in that even though there are already almost 30 different available HIV drugs, treatment often fails or is infeasible in poor nations, and thousands of patients die every year in even the wealthiest nations. HIV's 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 such 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 that HIV research is becoming more closely tied to the specific conditions in poor nations and regions. Finally, there is the seemingly low-technology requirement to create reliable microbicides, which could prevent transmission through sexual behavior, even if these products cannot defeat HIV itself (Coplan, Mitchnick, and Rosenberg 2004).

Can the Stakeholder Model Work?

We believe that the stakeholder model is fundamentally flawed because it would blunt new drug development and do little to help solve the problems that motivate its use.

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

We begin by noting that an essential feature of a stakeholder model, which is 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 and other stakeholders is wide (Reisel and Sama 2003, pp. 374, 381). These gaps apply not only to prices but also to the kinds of drugs to develop (so-called me-too drugs, or new members of an existing therapeutic class, as opposed to 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 that occupy 5 to 15 years, entry and exit may alter the complexion of the industry itself. Even informal enforcement of broad understandings (e.g., to pursue a certain line or research) may prove impossible. If understandings were sufficiently concrete to provide a guide to future behavior, it would be difficult 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 in the pressure of events. If manufacturers succeed in developing products that the other stakeholders want (e.g., a malaria vaccine), they will have created a new situation that requires a new agreement about pricing and distribution. These negotiations are likely to be resolved at price levels that, though 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). That reasonable people may disagree on how much profit is needed as an R&D incentive greatly complicates the situation (see Goozner 2003; Reisel and Sama 2003, pp. 370, 372).

The Stakeholder Model Versus Pharmaceutical R&D

Even if stakeholders could reach fundamental agreement that would persist in the tumult of politics and marketplace, another equally fundamental difficulty arises. In general, the consenses envisioned for the stakeholder model pertain to pricing, marketing, distribution, and so on, for drugs that already exist. However, if the stakeholder model is to work, it must be forward looking. Manufacturers must be able to foresee stakeholder agreements and informal understandings years in advance 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 need 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 that Wennberg, Fisher, and Skinner [2002] describe and the striking international variations in the use of antidepressants that Fleming and Morice [2004] describe), and, most important, the compensation that governments and organizations will provide for what has been developed. Unfortunately, it is difficult to imagine the concrete principles that can be expected to apply when challenging drug research is finished (see Reisel and Sama 2003, p. 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 that the stakeholder approach will overcome these difficulties? Would it promise to yield sufficient foreseeable profits to bring forward the drugs on 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 agreed that the world needs better TB drugs and a strong malaria vaccine. Close observers also agree that

if such products were developed, the associated intellectual property would not be respected, and the firms developing the products could not expect to earn a profit that was commensurate with the financial risks (see Kremer 2002). Parties who want to be included among the stakeholders in pharmaceutical research envision a world in which the payoffs for the development of new drugs would fall far short of compensation for R&D investments. Publicly financed investment, which could come in various forms, would become the primary source of new drugs (Hubbard and Love 2004). Recognizing the insecurity of intellectual property for drugs targeted at diseases endemic in developing nations, Michael Kremer and others propose 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 issues are important. In a stakeholder-dominated world, parties with no direct financial stake would strongly influence or even make decisions ranging from R&D to manufacturing, testing, drug therapy, and investment in infrastructure. The absence of a market test for these activities invites inefficiency. In the traditional nonstakeholder world, the market penalizes failure even as it rewards success. Persistent attention to the pharmaceutical industry's profits tends to obscure the essential role of industry losses in drug development. 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 absorbing the costs of failure, which Merck did when four late-stage drug candidates failed in 2003, despite the firm's formidable reputation in pharmaceutical research (Landers and Lublin 2003).

Equally important are the tasks of manufacturing, distribution, and drug therapy. The mixed record of the impact of 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. An article in *The Economist* (2004, p. 79) 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 subsequently 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.

It is assumed that international organizations would undertake most of the work involved in distribution and use of pharmaceuticals, but the stakeholder model presumably involves far greater participation by pharmaceutical firms in such arduous and costly tasks. It is difficult to know how much firms would be expected to do to ensure access and proper usage, in addition to supporting and even participating in public health training and enterprises. It is clear that such activities are essentially unlimited in their scope and expense, which raises serious questions about the financial burdens associated with vigorous pursuit of the stakeholder

model for the pharmaceutical industry. Without an available practical example, it is difficult to assess such basic matters as the types of activities and costs that would be associated with the stakeholder model.

The Stakeholder Model Applied to HIV/AIDS

The HIV/AIDS crisis provides an excellent opportunity to explore how the stakeholder model would work at a practical level and to illustrate the fundamental difficulties in such an approach.

What Is the Consensus?

The pharmaceutical industry continues to develop new HIV drugs as older ones encounter the inevitable problem of drug-resistant HIV strains. The industry trade organization PhRMA (2003) lists approximately 80 HIV drugs and vaccines in development, despite more than a decade of criticism and a shift in the locus of the epidemic from wealthy to poor regions, which has undoubtedly deterred some firms from entering a market characterized by indifferent returns and difficult public relations. We and other researchers have often been informed privately that large firms have refrained from entering the HIV/AIDS market and indeed are relieved that they had not done so earlier. Bate (2003) documents that 27% fewer companies were working on antiretroviral 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 we discuss subsequently). Nonetheless, intense criticism of the industry continued at the July 2004 Bangkok conference, where the Pfizer chief executive officer and the chief of the U.S. AIDS program were booed by the audience when they prepared to speak (Mader 2004). Much of the criticism focused on the United States' (by far the largest funder of HIV/AIDS programs in sub-Saharan Africa) waiting for FDA approval of new combination generic drug formulations rather than immediately purchasing generic brands that were already approved by the WHO through less thorough scientific assessments (Bate and Tren 2004). Both activists and mainstream international HIV/AIDS organizations have rejected the idea that either the United States or other organizations should purchase branded drugs rather than the cheapest available generics. This rationale, which eliminates industry profits from serving the needs of poor nations, leaves no room for a consensus that includes the industry itself.

Other signs also suggest that stakeholder consensuses will not be easily forged. The industry has engaged in several initiatives in support of public health activities, including AIDS-related operations. For example, Merck has entered into arrangements with four African countries including Botswana, where Merck and the Gates Foundation have each given \$US50 million over five 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 in Kampala. That operation is run by the Academic Alliance for AIDS Care and Prevention, for which U.S.

experts train doctors, nurses, and others to treat infectious diseases. However, there is little reason to believe 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 that involved several pharmaceutical firms and UNAIDS, which was launched in May 2000.³ Improvement of HIV/AIDS prevention, treatment, and care was sought by AAI. Success was mixed, as it involved drug industry involvement in activities for which the group had no particular expertise or comparative advantage. Drug activists dismissed the AAI as a public relations exercise by drug companies and accused the companies 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).

It might be assumed that when a manufacturer decides to provide a necessary drug at low prices, or even for free, construction of a consensus on whether or how to use the drug would be relatively straightforward. Unfortunately, this is not necessarily the case. An illuminating example is the tortured deliberations and false starts that accompanied the introduction of a superior combination malaria drug in Kenya in the late 1990s (Shretta et al. 2001). The most difficult issues—drug resistance, the impact on the overall health system, infrastructure requirements, and so on—are familiar themes, but the difficulties are far greater when HIV/AIDS drug treatment rather than treatment of malaria is considered.

These developments, which range from small-scale activities to massive changes in prices and intellectual property protections, do little to suggest that a broad consensus or understanding is likely to emerge with the force and stability necessary to support a stakeholder approach to the role of the pharmaceutical industry in HIV/AIDS. Rather, a consensus would leave pharmaceutical firms with little role beyond developing new drugs and then essentially giving them away.

HIV Drug Patents in Africa

With the possible exception of drug prices, no topic in the worldwide HIV/AIDS epidemic has been more contentious than patents, especially in sub-Saharan Africa. Much of this was triggered by a 1998 lawsuit that was 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 (*The Wall Street Journal* 2001), obscured two essential points.

First, the industry's primary motive in the patent litigation was apparently to maintain its intellectual property rights, not so much with the idea of supporting prices as to maintain control over trans-shipment from low-price to high-price countries (PhRMA 2001). Second, on the whole,

HIV drug patent rights have been indifferently sought or awarded, and they have had negligible effect. With a few exceptions, HIV drug patents have been 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 when 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 (see *The Economist* 2003; TREAT Asia 2004). In addition, some companies, such as GlaxoSmithKline and Bristol-Myers-Squibb, have entered into voluntary license agreements that allow generic drug companies to produce copies of their patented drugs (Zimmerman 2001).

R&D Incentives

We have described the wide range of R&D activities that are 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 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. However, there are also two ways that the stakeholder approach could undermine R&D.

The first pertains to the question of how prices and profits can be realized after firms develop innovative drugs. Economic demand from the populations of sub-Saharan Africa is extremely small. However, there is strong potential demand from the organizations funded by the wealthy Western nations and individuals. These organizations, which range from the U.S. government to WHO, the World Bank, and the Gates Foundation, could provide the 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 generic 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. South Africa was one of the few African nations that had a large and profitable research-based pharmaceutical sector. In the past decade, South Africa has experienced a gradual decline of pharmaceutical manufacturing, 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 shown, 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 long-standing inward-looking

³The companies involved are Boehringer-Ingelheim, Bristol-Myers-Squibb, GlaxoSmithKline, Merck, and Roche.

pharmaceutical industry has become prominent in the world generic drug market. The Indian pharmaceutical industry has also begun to move aggressively into original research, using that vast country's reservoir of technical talent, but it is evident that this development relies on the establishment of patent rights and the prospect of profits rather than on a new stakeholder consensus (Slater 2003).

Bottlenecks and Drug Access

If international agencies and sub-Saharan Africa governments had been ready to use HIV treatments when they became affordable, there would have been a swift expansion in HAART for the several million HIV victims whose CD4 counts indicated that they were ready for drug therapy. Many surveys have found that this did not occur after drug prices plummeted and generic manufacturers entered. There are several reasons for this.

In some cases, national governments simply refused to pursue HAART. Perhaps the most remarkable example occurred in South Africa, where, in 2001, the health minister announced to a shocked crowd of AIDS activists that she did not intend to distribute the generic drugs that had just become available after the industry litigation over drug patents was settled (Schoofs 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 they believed that antiretroviral therapy would do more harm than good. The minister recently reaffirmed a long-standing position opposed to widespread use of antiretrovirals to prevent prenatal HIV transmission, recommending breast-feeding instead (*Business Day* 2004; Cauvin 2001). Previously, the minister had stated that she would not support the use of antiretroviral drugs in government-run hospitals until monitoring and care matched the standards of western European hospitals (*New York Times* 2001).

In other countries, the problem has not been hostility toward HAART but an inability to take advantage of drugs and supporting funds when they become available. The evidence from Botswana is that political will and bureaucratic competence is 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% of people for whom HAART is indicated (Gayle and Lange 2004). This is despite large increases in spending and 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 Global Fund's standards for performance-based disbursement (Brugha et al. 2004).

This is not to say that these nations should simply plunge ahead with using any available drugs, which would do more harm than good by accelerating drug resistance while helping few victims. These nations face difficult choices when they decide on mass HIV drug treatment, and these choices involve substantial commitments, including recruiting 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 the elements is that pharmaceutical firms will do much more than just develop, manufacture, and market drugs. They also serve as sources of expertise, funding, and perhaps even personnel for the larger tasks of delivering and administering drug therapy and associated activities such as diagnostics and monitoring.

This raises two difficulties. The first 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 is likely to be large, as is evidenced by the slow pace of HAART in places in which considerable sums are already being spent. There seems to be little reason to saddle these costs on pharmaceutical firms because they bear no relationship with industry resources. It might be asked how the industry could supply the needed sums, given the presumed lack of profits from HIV drugs. The answer is, profits from drugs sales in other regions and for non-HIV products. This reasoning suggests that as a stakeholder model becomes more likely, the financial incentives for exiting the HIV/AIDS market altogether become stronger.

The second 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. (Good governance, the other element, is discussed subsequently.) Although considerable public and nonprofit resources are spent on vaccine development, the historical record in such activities as TB and malaria suggests that there is little likelihood that the solution will emerge from that sector; R&D is the supreme comparative advantage of the private pharmaceutical sector.

However, 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 countries, the industry does not perform the bulk of routine activities such as storage and distribution, leaving much of that to specialist wholesalers. Pharmaceutical firms are traditionally distant from the actual use of all but a few specialty drugs. In the far more difficult circumstances of treating HIV/AIDS in poor nations, industry expertise is even less relevant. Given such needs as cold storage for many HIV drugs, it might make more sense to involve large fresh grocery chains, such as Tesco, or rely on agencies with a good track record, such as International Healthcare Distributors in South Africa. Regardless, 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, which is estimated at slightly more than one-third of the adult population. We noted previously that the pharmaceu-

tical firm Merck, along with the Gates Foundation, has offered tens of millions of dollars for HIV/AIDS work. To date, the efforts in Botswana have been highly successful, though less successful than the country's leadership had hoped. By June 2004, many HIV/AIDS clinics had been built, and approximately 15,000 Botswanans were receiving treatment. (This was well under the government's goal of 60,000 people, presumably because of a combination of stigmatization, ignorance, or inaccurate estimates of the HIV-positive population.) Despite these successes, most of the government's AIDS budget remains unspent (Attaran 2004). Despite Merck's cash and in-kind contributions, Botswana wisely uses many non-Merck drugs while employing several different triple therapies. The success of this enterprise depends not on pharmaceutical expertise but on organizational skills, political will, and continued funding from available sources.

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 believed to be an inevitable consequence of governance that often barely reaches rudimentary levels.

Several signs suggest that dramatic progress against HIV/AIDS may need to await improvements in governance. On the whole, the nations that have experienced striking improvements in how they are governed (i.e., Uganda and 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 one of the largest HIV-positive populations 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 (*Sunday Times* 2004). However, the overall health infrastructure, including higher-level medical staffs and educational facilities, remain severely underfunded as many of the best personnel migrate to wealthier countries. 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.

Conclusion: The Dangers of Abandoning the Traditional Profit-Motivated Model

It is natural that the worldwide HIV/AIDS epidemic would focus critical attention on the pharmaceutical industry. The industry's 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 that prohibit patent abridgment. That HIV/AIDS migrated rapidly and relentlessly from wealthy countries to the poorest regions brought all these factors into sharp relief. That the greatest beneficiaries of future research breakthroughs would be the world's poorest people dictates that the preser-

vation 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, resistance to reasonable HIV therapy by governments, and severe administrative bottlenecks that have nothing to do with drug pricing or availability. Also evident is that much R&D remains to be done in the use of available drugs 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: remove patent rights, request cost-based drug supplies, or permit free licensing to generic manufacturers. At the same time, there has been a firestorm of criticism of the pharmaceutical industry in a much broader context, focusing on price disparities among wealthy countries and on the high costs in developed economies of both R&D and the products generated by R&D. The outcome has been proposals for a new approach to the drug industry, involving not only changes in public policy but also the remarkable idea that the industry itself should adopt a stakeholder model to replace the traditional capitalist, profit-driven stockholder model.

Although the stakeholder model is hardly well-defined, its essential elements raise serious problems, including 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 difficult to imagine what the terms of a stakeholder approach might be, how that approach could help solve the problems facing poor nations, or how it could help generate the new medical technology—especially an HIV vaccine—that is desperately needed and is least likely to emerge from the government or nonprofit sectors.

A 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 countries, providing progressively less help to the poorest nations as their respective HIV populations steadily diverge. A situation parallel to that prevailing for malaria and TB would occur, in which the drugs sufficient to treat the few victims in wealthy countries are of limited use in the countries in which victims number in the millions and in which no new TB drugs have been introduced in decades. The stakeholders will be left with little to show for abandoning the traditional drug development model.

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