

Access to HIV Treatments in Developing Countries Case Summary

M.J. Peterson with research assistance by Osman Kiratli and Sarah Kiester
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Growing awareness in the 1990s that HIV and AIDS were more prevalent in developing countries than in industrialized ones and that effective treatments were available to only a few patients because of limited government and personal incomes, transformed HIV/AIDS advocacy efforts. Pressuring governments and pharmaceutical companies to ensure provision of treatment to larger numbers of HIV-infected persons (often called "HIV-positive persons" or "persons living with HIV") became a priority. The high prices of HIV medications were quickly identified as a major barrier to access, and became the subject of a significant ethical contention, which continues to this day. After providing background on the treatment of HIV infection, this case will summarize the key features of the ethical contention.

Treating HIV Infections

HIV, Human Immunodeficiency Virus, destroys a person's immune system by systematically destroying CD4+ type T cells. Left untreated, HIV infections follow this progress:

1. initial acute HIV infection, occurring 2-4 weeks after exposure to HIV establishes an infection (sometimes but not always marked by flu-like aches and fevers, which then abate),
2. asymptomatic HIV infection, lasting about 9 years on average after the initial acute infection abates, during which the person appears healthy because the immune system has not yet been weakened significantly,
3. early symptomatic HIV infection where the immune system is sufficiently weakened that other infections occur more often and more severely than in persons with healthy immune systems,

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4. Acquired Immune Deficiency Syndrome (AIDS), marked by such severe compromise of the immune system that the person dies from one or more "opportunistic infections" that take advantage of the immune system's weakness to catch and spread in the body.¹

Initial hopes that HIV could be cured by a medicine that would cancel its effects or prevented by a vaccine that would give people immunity to it have been disappointed so far. These hopes were and are sustained by the existence of "non-progressives," individuals whose initial acute HIV infections faded and then remained asymptomatic for the rest of their lives. Though clinical trials of an experimental vaccine in Thailand during mid 2009 showed significant promise, both vaccines and cures remained distant prospects in January 2010.²

The vast majority of persons infected with HIV can hope only to slow down the course of CD4+ cell destruction and maintain a functioning though weakened immune system through continuing drug treatments. These drug treatments are complex because simultaneous doses of several drugs are required to slow down the course of infection. The current forms of Antiretroviral Treatment (ART) typically combine three drugs: 2 nucleoside analogue reverse transcriptase inhibitors (NARTIs or NRTIs) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). NRTIs slow the spread of HIV in the patient's body by reproducing a faulty version of the virus's genetic material. NNRTIs prevent HIV's reverse transcriptase enzyme from reproducing itself by binding to the virus's protein.³ PIs keep protease molecules from breaking the particular HIV proteins that become more effective disease agents in smaller pieces. Any particular mix of drugs loses effectiveness over time, requiring patients to shift medications periodically. Since each drug also has side effects, patients on ART often suffer from nausea, headaches, weakness, malaise (a general sick feeling), and fat accumulation on the back and abdomen. Long courses of treatment also increase the risk of heart attack. Infected persons also need to monitor their condition with blood tests checking CD4+ counts and levels of HIV infection (by measuring HIV RNA level, which indicates how much virus is in the blood) every 3 to 6 months. The goal of treatment is to keep the CD4+ count from dropping further, and to reduce the HIV viral load to an undetectable level. In sum, effective treatment of HIV requires provision of three elements: an initial test to determine whether the infection is present, combination drug therapy to slow its development, and periodic testing to determine whether the drug therapy is continuing to work or needs to be modified.

Treating HIV is complicated by features of the virus. First, it occurs in two major variants, designated HIV-1 and HIV-2 respectively. HIV-1 is more prevalent; HIV-2 can remain asymptomatic for longer periods but is harder to treat because it is resistant to more antiretroviral medications than HIV-1. Both variants also have distinctive sub-strains, with varying resistance to medications. HIV-1 appears in two main forms, Types A

¹The US National Institutes of Health provides good basic information about HIV and AIDS in its MedLine Plus online encyclopedia. First consult the general entry on AIDS (<http://www.nlm.nih.gov/medlineplus/ency/article/000602.htm>), then more detailed entries about the successive stages of its normal progression (<http://www.nlm.nih.gov/medlineplus/ency/article/000604.htm>, <http://www.nlm.nih.gov/medlineplus/ency/article/000682.htm>, <http://www.nlm.nih.gov/medlineplus/ency/article/000603.htm>, and <http://www.nlm.nih.gov/medlineplus/ency/article/000594.htm>).

²Marchione, Marilyn and Michael Casey. Study gives new hope for AIDS vaccine." *The Star* (Toronto) 24 Sept. 2009. <http://www.thestar.com/article/700251> (accessed 2 April 2010).

³ AIDS Info. U.S. Department of Health and Human Services. www.aidsinfo.nih.gov/

and B. A and B are further divided into subtypes, groups, and strains. Some are quite difficult to treat. One of the worst, a mutant version of HIV-1-B, designated 3-DCR, was identified in 2005. It is resistant to many antiretroviral medications and produces fast-progressing infections leading rapidly to AIDS.⁴ 3-DCR illustrates the complex relations between viruses and their human carriers; the person whose blood tests led to identification of the strain had engaged in unprotected sex with multiple partners and was also using methamphetamine, a powerful stimulant that is illegal in most countries. Thus a particular HIV-infected individual's prospects also depend on which sub-strain is contracted at the time of exposure.⁵

Developing countries, where HIV is most widespread, face the greatest obstacles to providing treatment. They typically have to contend with lack of sufficient medical facilities for performing initial and follow-up testing, inadequate medicine distribution and storage facilities, HIV-infected persons who have difficulties understanding and following ART consistently, and the high cost of ART medications in relation to local incomes or government health budgets. Since combination ART, which simplifies treatment by providing all three medications in a single pill, became available in 1996 there has been significant progress in dealing with all of these obstacles. However, the activists' goal providing every HIV-positive individual with constant access to effective ART is yet to be attained.

When HIV was first identified as the underlying cause of AIDS in 1982, the basic physical mechanisms of T-cells' role in the immune system had just been worked out and the particular way HIV reacted with CD4+ cells was not understood. By 1985, it was understood well enough for CD4+ cell counts to identify persons infected with HIV.⁶ However, few people were tested, partly because being HIV-positive carried heavy social stigma and partly because the tests were too expensive to use in developing counties. These limits on initial screening inspired development of an indirect way to identify HIV-positive individuals by observing the presence of other infections that individuals with healthy immune systems shake off easily. In the form established by the World Health Organization (WHO), HIV infection is defined as having four stages:

- Stage I: HIV infection is asymptomatic;
- Stage II: minor mucocutaneous manifestations – including rashes or skin lesions -- and recurrent upper respiratory tract infections;
- Stage III unexplained chronic diarrhea lasting more than a month, severe bacterial infections, and pulmonary tuberculosis;
- Stage IV: (AIDS) toxoplasmosis of the brain, candidiasis of the esophagus, trachea, bronchi or lungs, and Kaposi's sarcoma.⁷

⁴ Reported in *Nature Reviews Microbiology* 3 (5): 370 (May 2005). The article noted the patient's drug use but did not directly suggest that this habit may have contributed to the mutation.

⁵ See "HIV types, subtypes, groups and strains" at <http://www.avert.org/hiv-types.htm> (accessed 27 March 2010).

⁶ The science is summarized in A. S. Fauci and others. 1984. "Acquired Immunodeficiency Syndrome: Epidemiologic, clinical, immunologic, and therapeutic considerations." *Annals of Internal Medicine* 100: 92-106.

⁷ World Health Organization, 1990, revised 2005, available at <http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf>

Because it relies on observing infections that occur only after a person's immune system is compromised, detecting HIV in this way meant that many HIV-infected persons started receiving ART too late for it to be fully effective. Expanded multilateral and bilateral aid programs initiated after 1996 helped developing countries to expand HIV testing and treatment facilities and follow the guidelines on providing ART developed by the United States Centers for Disease Control in 1990. Under this system HIV-infected individuals are put on ART when their CD4+ cell count falls below 500 cells per microliter of blood (500/mL),⁸ and as suffering from AIDS when their CD4+ cell count drops below 200 cells per microliter (mL) of blood. Though some HIV-infected individuals, including pregnant women and persons with HIV-related kidney or neurological problems, are put on ART as soon as an HIV infection is detected, for most the start of treatment is timed to coincide with the onset of early symptomatic HIV because of the medications' strong side effects.

Developing country health services also developed more effective information campaigns in the late 1990s and early 2000s. Some address slowing or preventing the spread of HIV by providing information about how infection is transmitted and measures individuals can take to reduce their risk of exposure. Contrary to the impressions circulated when HIV first emerged, infection is not spread by skin contact or saliva. It is now well understood that infection is transmitted from person to person primarily through a) sex acts (including oral and anal sex), b) transfusions of HIV-contaminated blood, c) use of HIV-contaminated needles for injecting drugs, and d) pre- or post-natal transmission from infected mothers to newborns. Greater awareness of the disease pathways have helped slow down the spread of HIV, reducing the number of new cases encountered each year. Other information campaigns help HIV-infected individuals understand why ART has been prescribed, what it involves, and the importance of taking the medications and getting the follow-up blood tests consistently. Patients' ability to follow their therapy has been increased as pharmaceutical companies, both the major innovating firms producing the patented medicines and the generic manufacturers producing equivalent drugs, developed versions of combination ART taken in a single daily dose (the "once a day pill"). Administering ART in warm countries where electricity is not always reliable or even available has been facilitated by development of heat-resistant versions of the drugs.

The annual per patient cost of administering ART has declined considerably. The \$10,000 per person per year cost prevailing in the USA in 1995 before combination and once a day therapies was reduced to about \$350 in 2001 as activist pressures everywhere for lower prices and generic production opened up. By mid-2007, the cost had dropped to about \$100 per person per year for "first line" ART using medications developed in the mid-1980s. However, drug-resistant variants of HIV needed to be treated with newer "second-line" drugs, most of which were still covered by patents and all of which are more expensive than the "first-line" treatments. In 2007, the least expensive generic form of second-line ART treatment preferred for use in developing countries, a heat-stable combination using lopinavir and ritonavir, cost \$695 per patient per year.⁹ AIDS activists and others began warning about the price implications of having to shift to "second-line" drug combinations in 2004 and continued exerting pressures on governments and drug makers to reduce the prices as much as possible.¹⁰

⁸CDC Guidelines available at <http://www.cdc.gov/mmWR/preview/mmwrhtml/00054080.htm>. The CDC also maintains its earlier definition of AIDS as present when a patient suffers from an infection uncommon in persons with healthy immune systems.

⁹Robert Weissman. 2007. "Big pharma and AIDS : Act II," *Multinational Monitor*, March/April 2007, p. 21

¹⁰ E.g., *Medecins sans frontières* 2004.

The Contention Over Drug Patents

Attacks on drug patents have been a prominent feature of campaigns against high ART prices. As Michael Hagmann put in 2002, “The major obstacle to increased drug access – though not the only one – is patent royalties.”¹¹ Health GAP, an activist organization, is even more vehement; in its view “the human right to life and to health must prevail over the pharmaceutical industry’s excessive profits.”¹² This has been a very attractive argument because patents do create artificial monopolies on production by allowing the patent holder to decide whether to let others use the advance covered by the patent by giving them a license and what to charge anyone granted a license. Patent systems in the industrial countries had long included drugs among the innovations that could be patented, and in both the 1980s and today give the inventor a 20-year monopoly on production and sale of the product protected by the patent. These limited-duration monopolies had become central to the economic calculations of two sets of innovator pharmaceutical firms: major manufacturers like Bristol-Meyers Squibb, GlaxoSmithKline, or Hoffmann-LaRoche that maintain their own research departments and produce the drugs their researchers develop themselves, and a set of smaller firms that specialize in drug development and license other firms with production facilities to manufacture the drugs they develop.

The controversy over patents became so intense because the continuing lack of either a preventive or a prophylactic vaccine against HIV means there is no alternative to long term ART. Thus, AIDS activists (who include both persons suffering from HIV infections or AIDS and noninfected supporters) have complained vociferously about prices and demanded that ART be available to everyone who needed it regardless of income. They have been joined by healthcare access advocates defining access to “essential medicines” – or to healthcare more generally – as a human right in campaigns for elimination or stringent limitation of drug patents. The campaign against patents on ART therapies was also quickly linked to the already-initiated transnational campaign against the expansion of intellectual property rights included in the 1994 Agreement on Trade-Related Intellectual Property Rights (TRIPS). TRIPS is one of several agreements addressing specific concerns developed during the Uruguay Round of international trade negotiations that produced the World Trade Organization and a revised General Agreement on Tariffs and Trade. It is also one of the agreements that all states joining the WTO are required to accept as part of their membership. Industrial countries had to implement TRIPS immediately while developing countries were allowed transition periods before they had to implement TRIPS by revising their patent law and enforcing the new rules. Some developing countries, including Brazil had a 5-year transition period, meaning they would have to start implementing in 2000. Most developing countries, including India, had a 10-year transition period. The least developed countries were allowed a longer transition, one currently scheduled to end in 2016.

The main argument in favor of patents is that they serve the general interest by promoting invention and speeding up the process of turning inventions into marketable products. The underlying economic calculation is that the long term gain to society as a whole more than offsets the benefits of the temporary monopoly enjoyed by patent holders during the term of their patents. This proposition has been contested among economists (though more intensely in the field of copyright because computer software has been

¹¹ Michael Hagmann. 2002. “World Trade Organization still threatens supply of affordable AIDS drugs.” *Bulletin of the World Health Organization* 80(9): 762.

¹²Health Global Access Project. “About Health GAP.” <http://www.healthgap.org/about.htm> (accessed 29 April 2010).

treated as a form of expression rather than a material thing). So far their arguments have not been accepted widely enough to overturn whole patent systems, though particular points have inspired modifications to limit the sorts of things that can be patented.

However, the concerns about access to HIV treatments are focused primarily on the immediate to medium term, about providing medications to persons identified as needing them. Although the lifetimes of HIV-infected persons have been extended with ART, everyone knows that without ART their lives would be much shorter and much more miserable once the early symptomatic phase sets in. Those who oppose compulsory licensing or other forms of weakening drug patents have not been able to challenge the need for the medications; they have been limited to using a longer-term argument, that abolition or large-scale overriding of drug patent rights will not be helpful in the long term because it will inhibit the continuing innovation needed to develop anti-retroviral therapies as HIV mutates in response to current treatments.

The contention over ART prices and patents played out in two major rounds. The first, running from 1996 through roughly 2002, initially involved AIDS activists in industrial countries, particularly ACT-UP (AIDS Coalition to Unleash Power) in the USA, who attracted broad public support for their efforts to bring down the prices of the first-line antiretroviral therapies. As awareness of HIV prevalence in developing countries increased, the campaign went transnational, with local activists and governments in developing countries also seeking ways to bring down the price. This second round of contention, which arose in 2004-2005 and continues today, involves efforts to ensure that prices of the newer second-line treatments are kept as close to those of the older first-line ARTs as possible. In both phases, the AIDS activists and other campaigners have used a "patients versus profits" framing that casts the major innovator drug firms as the main source of the problem. Activists have also used human rights rhetoric to prod governments as well, advancing the linked claims that governments have, and should take up, a duty to distribute ART to everyone who needs it, and that governments taking up that task should be able to acquire all the medications they need at prices they can afford. Both the "patients versus profits" and human rights framings have been extremely effective. They present the issue in a particular light and guide audiences thinking toward the activists preferred solutions by presenting those solutions in a context in which they appear to be uncontested common sense.¹³

Thus, it is not surprising that activist pressure elicits wide public support in both industrial and developing countries. This has put the leading pharmaceutical companies in a position where they have been constrained to lower prices. Economists point out that having different prices in different markets causes problems by encouraging parallel trading – buying large amounts of a product in the lower-price market and then selling them in a higher-priced market – that make unusually high profits for those engaged in the trading while siphoning supplies from the low-cost market to the higher-cost market. The likelihood of parallel trading is low (though not eliminated¹⁴) with ART medications since they are typically bought by or on behalf of government health services in quantities related to domestic need.

¹³ Sidney Tarrow 1998 *Power in Movement: Social Movements and Contentious Politics*, Chapter 7 (2nd Edition, Cambridge: Cambridge University Press) provides a good summary of research on the importance of effective framing for activist success. Margaret Keck and Kathryn Sikkink 1998 *Activists beyond Borders: Transnational Advocacy Networks in International Politics* (Ithaca, NY: Cornell University Press) remains one of the leading applications of the ideas to transnational issue campaigns.

¹⁴ Corrupt officials have diverted government-purchased shipments into their own countries' private markets.

Round One

The first round of contention occurred in the interval between adoption of TRIPS and its extension to major developing countries. This fortuitous timing made it much easier for the government of Brazil to adopt an ambitious program of providing antiretroviral therapy to every HIV-positive person in Brazil regardless of income in 1997 because it was able to acquire generic versions of the necessary drugs. Until 2000 neither Brazilian nor foreign firms were constrained to respect anyone else's drug patent in deciding what to make for the Brazilian market. Between 2000 and 2005 the Brazilian government could also continue to import from Indian generic makers because India was not obliged to protect foreign drug patents. Brazilian demand for generic ART pressed prices downward in three ways. First, that demand helped Indian generics makers increase their manufacturing capacity, realizing economies of scale that got passed along in power prices. Second, the new scale of their operations also inspired an expansion in the production of, and hence lower prices for, the active pharmaceutical ingredients needed to make antiretroviral medications. Third, Brazilian threats to issue compulsory licenses on patented drugs combined with the size of the overall Brazilian drug market meant the government could secure price concessions from patent-holding firms seeking to limit the fostering of competitors that would occur if compulsory licenses were issued.

UN agencies become more involved in HIV/AIDS issues during 1996 with creation of the Joint United Nations Programme on HIV/AIDS (UNAIDS). AIDS received high-level political attention at the May 2000 meeting of the World Health Assembly, the primary decision-making body of the WHO, which directed the staff to develop a global plan for combating HIV. This was a significant reversal for WHO, which had dismantled its separate AIDS office in 1995 in anticipation of shifting those activities to UNAIDS. The heads of state and government who met at the UN-organized Millennium Summit in September 2000, stated a commitment to slowing the spread of HIV and broadening access to treatment in the Millennium Development Goals. Specifically, Goal 6 on combating HIV/AIDS, malaria, and other diseases sets targets of a) halting and starting to reverse the spread of AIDS by 2015, b) achieving universal access to HIV/AIDS treatments for all who need them by 2010.¹⁵ The UN General Assembly followed with a Declaration of Commitment on HIV/AIDS in September 2001 and a follow-up Political Declaration on HIV/AIDS in June 2006.¹⁶ While these statements had no immediate effect on the prices of ART, they did indicate that HIV and AIDS were considered important enough problems to receive attention at the highest levels of government, and that UN approaches to HIV/AIDS would be defined within a strong human rights-oriented framing of the problem.

These statements provided a broader political context within which individual governments pursue their policies on AIDS. Brazil, in particular, persisted in its commitment to provide ART to all individuals who needed it regardless of income. This meant the Brazilian health service was purchasing significant quantities of ART drugs. The extent of the Brazilian market was a significant factor in the decision by Indian generics maker Cipla to offer ART for approximately \$395 per patient per year in mid 2001. This accomplishment put significant pressure on the major drug companies to reduce the prices of their

¹⁵ The text of the Millennium Development Goals is available through <http://www.un.org/millenniumgoals/aids.shtml> (accessed 29 April 2010).

¹⁶ General Assembly Resolution S/26-2, annex adopted on 27 June 2001 and General Assembly Resolution 60/262 adopted on 2 June 2006 available at <http://www.un.org/documents/resga.htm> (accessed 29 April 2010) and in Appendix B.

products. Activists were not shy about demanding lower prices or about shaming the major drug companies whenever they attempted to protect their patent rights. The 39 drug companies that had been trying to sue the South African government for patent violations because of its decision to permit domestic production of generic AIDS medicines abandoned their efforts in April 2001. One of the firms involved, GlaxoSmithKline, then licensed Aspen, a major South African generics producer, to produce designated quantities of their patented AZT, 3TC and Combivir without royalty charges.¹⁷

Continuing pressures on drug companies created the second form of response: tiered pricing based on a country's presumed ability to pay. In mid 2001, the major pharmaceutical firms participating in the Accelerated Access Initiative agreed to a "tiered" pricing system. Governments and individuals in industrial countries would pay full price for the drugs; governments and individuals of the higher income developing countries would get a discount of about 30%; governments of least developed countries would get a 90% discount.¹⁷ Developing countries also receive assistance in the purchasing process through the Group of 8's Global Fund for AIDS, Malaria, and Tuberculosis, UNITAID established by a coalition of European and other governments, the USA's PEPFAR, and the Clinton Foundation.

By then policy analysts were considering the balance that should be struck between intellectual property rights, profits, and patient needs and offering various ways of modifying normal market practices to better serve the latter without completely ignoring the former. Amir Attaran and Lee Gillespie-White proposed a deal in which governments would respect patents and in return pharmaceutical makers holding the patents would provide HIV drugs to the "global poor" at break-even prices. If that could not be arranged, they advocated either limiting patentability of certain medications, including HIV treatments, in the poorest countries or developing an industry practice of issuing licenses to generics makers sufficient for them to supply poor countries.¹⁸ Udo Schenk and Richard E. Ashcroft preferred starting with compulsory licenses because they believed these were the most effective way to reduce drug prices.¹⁹

The first round of contention about ART prices also became an element in the ongoing campaign by transnational activist groups to secure abolition or significant revision of the TRIPS Agreement. Abolition was unlikely. TRIPS is generally presented by antiglobalization activists as a scheme hatched by Western (particularly US) firms to maintain their dominant positions in the global economy, but innovative firms in a number of the more advanced developing countries also supported extensions of intellectual property rights.²⁰ Yet even governments and firms supporting the basic TRIPS rules were willing to consider proposals for certain revisions.

¹⁷ The UN Conference on Trade and Development maintains the agreed list of least developed countries. There is no single list of developing countries, but for most purposes the countries in the high middle income and low middle income lists of the World Bank's classification of economic levels are regarded as developing. See World Bank classification at <http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS/0,,contentMDK:20420458~menuPK:64133156~pagePK:64133150~piPK:64133175~theSitePK:239419,00.html> (accessed 27 March 2010).

¹⁸ Amir Attaran and Lee Gillespie-White, 2001. "Do patents for antiretroviral drugs constrain access to AIDS treatment in Africa?" *JAMA: Journal of the American Medical Association* 286(15): 1891.

¹⁹ Udo Schuklenk and Richard E. Ashcroft. 2002. "Affordable access to essential medicines in developing countries: Conflicts between ethical and economic imperatives." *The Journal of Medicine and Philosophy* 27(2): 179-195.

²⁰ Including firms in India seeking to move from generics to more innovative products. See remarks of Satash Reddy, Managing Director of Dr. Reddy's Laboratories, quoted in K.S. Jayaraman, "Indian law could choke cheap drug supply," *Nature Medicine*

The campaign to reduce the impact of TRIPS on HIV medication prices was facilitated by the fact that this was a health issue. TRIPS already included provisions allowing governments to issue compulsory licenses for the production of patented medications in the event of a "health emergency." Though hedge buying a number of rules, the possibility of compulsory licenses didn't mean governments did not have to simply stand by and let pharmaceutical companies charge whatever they would, even in countries that do not normally set price controls for medicines. The problem with the initial version of compulsory licenses under TRIPS was that the government issuing the license could only authorize production for its own domestic market. This limitation was included to ensure compulsory licenses would not be used as a tool of industrial policy by giving domestic firms a competitive boost by letting them ignore patents.

However, one feature of the market for ART medications meant that compulsory licenses would not affect markets as trade lawyers anticipated. In the situations they typically consider, capacity to produce the good is fairly widespread and it is easy to find a domestic producer. However, many developing countries lacked production capacity and were unlikely to develop it very soon because they lacked necessary raw materials, sufficiently reliable and cheap energy, local demand sufficient to support economically competitive scales of production, and enough workers capable of engaging in quality drug production.²¹ Using their power to issue compulsory licenses would do those countries no good because they would not be able to find a domestic firm capable of using the license. It was therefore easy for AIDS activists seeking wider access to drugs and governments of developing countries seeking greater choice among suppliers to converge on proposals that TRIPS rules on compulsory licenses should be widened to include what trade lawyers call "parallel importing" – securing supplies of HIV drugs from generic drug makers in other countries. This requires agreement that governments without domestic production capacity could choose generic suppliers elsewhere and that governments with domestic capacity issuing compulsory licenses could extend those licenses to include production for other countries as well as for their own domestic market.

European governments had largely agreed with the idea by the summer of 2001,²² but the US government was resisting. However, the G.W. Bush administration handed activists the material needed for shaming it into agreeing in the fall. Information that it was considering using a compulsory license to secure sufficient supplies of Cipro, an antianthrax treatment covered by a patent held by Bayer, in the wake of the anthrax letter scares was widely reported in the US press. Though the US government eventually negotiated discount deals with Bayer instead, the discussion of using compulsory licenses allowed health activists and developing countries to paint US opposition to flexibility on HIV medicines as hypocritical and the US government backed off.²³ The coalition pressing for change was also able to muster enough support

11(5): 460 (May 2005) discussion of Indian firms attitudes available at [http://nopr.niscair.res.in/bitstream/123456789/2029/1/JIPR%2013\(5\)%20432-441.pdf](http://nopr.niscair.res.in/bitstream/123456789/2029/1/JIPR%2013(5)%20432-441.pdf)

²¹ Noted by Roger Bate. 2009. "When local production is not the answer," *The American: Journal of the American Enterprise Institute*, 2 September 2009. Available at www.american.com/archive/september/bernarticle.2009-09-01.0954500383 (accessed 4 March 2010)

²² Robert Watson. 2001. "European Union joins fight over drug patents," *British Medical Journal* 323 (#7303): 12.

²³ Daniel W. Drezner. 2006. *All Politics is Global: Explaining International Regulatory Regimes* (Princeton: Princeton University Press), p. 190. Contemporaneous reports included "A rush for Cipro and the global ripples" *New York Times*, 17 Oct. 2001, available at <http://www.nytimes.com/2001/10/17/world/a-nation-challenged-the-drug-a-rush-for-cipro-and-the-global-ripples.html?pagewanted=1>

among trade ministers to defeat an industrial country effort to include a limit that compulsory licenses be used only for drugs on the WHO's list of "essential medicines."²⁴

The November 2001 WTO Ministerial Conference in Doha, Qatar agreed to increase the "flexibility" institutionalized in government powers to issue compulsory licenses by allowing production under compulsory license not only for the local market but also for supplying any developing country that lacked domestic ART manufacturing capacity.²⁵ Though a declaration from a Ministerial Conference is a high-level political commitment, such commitments gain greater practical significance when they are incorporated into the formal rules. Incorporation soon followed. In 2003 the WTO Governing Council, the body of member state trade officials who manage the WTO in between Ministerial Conferences, issued a "general waiver" to Article 31 of TRIPS. This protected any member using the ministerial conference commitment against complaints that it was violating its TRIPS obligations in the WTO Dispute Settlement Process by making it a formal modification to the rules.²⁶ Then in 2005 the WTO formally proposed amendments to the TRIPS agreement that would convert the 2003 waiver into a stronger measure, a permanent exception specified within the TRIPS Agreement itself. Conversion will be complete when a sufficient number of WTO member states ratify the amendment. In the meantime, members can rely on the general waiver.

The change meant that any government – of an industrial state supplying developing countries with HIV medications as part of an aid program, of a developing country with domestic generics producers capable of supplying good quality HIV medications, or of a developing country seeking to import from generics makers in other countries – could issue a compulsory license and decide for itself on what royalties to pay the patent holder. However, the immediate effects of this change were limited. First, the Indian firms who were the world's major source of generic ART medications were not yet covered by TRIPS Agreement rules. Everyone was aware, however, that they would be covered starting in January 2005 when India's transition period ended. When that happened, Indian generics makers would not be able to make any HIV medication patented after 1995 – a date prior to the patents on most of the "second line" medications – unless they held a license from the patent holder or a compulsory license from a government.²⁷ Second, developing country governments did not rush to test the new rules because they were aware that both the USA and the EU were hostile to extensive use of the exception; Malaysia's November 2003 compulsory license to cover acquisition of three HIV treatments from Indian generics makers was the first to explicitly invoke the "Paragraph 6" rule.²⁸ Industrial and more advanced developing countries, including the EU, Norway, Switzerland, Canada, China, and South Korea, revised their patent laws to authorize granting compulsory licenses to domestic generics makers supplying developing countries.²⁹ However, only

²⁴Kristina M. Lybecker and Elisabeth Fowler. 2009. "Compulsory licensing in Canada and Thailand: Comparing regimes to ensure legitimate use of WTO rules." *Journal of Law, Medicine, and Ethics* 27(2): p. 230.

²⁵ World Trade Organization document WT/MIN(01)/DEC/2. Available from <http://docsonline.wto.org>.

²⁶ World Trade Organization document WT/L/540 and Corr.1. Available from <http://docsonline.wto.org>.

²⁷ "New patent laws may threaten India's supply of cheap antiretroviral drugs." 2005 *APBN* 9 (1 and 2): 39.

²⁸Drezner 2006, pp. 197-98 on US and EU attitudes; Patrick Mirandah. 2005/2006. "AIDS drug in compulsory licensing first," *Managing Intellectual Property*, No. 155, p. 93 (Dec. 2005-Jan.2006) on the Malaysian compulsory licenses.

²⁹ Lybecker and Fowler 2009, p. 227

Canada's program was tried to any extent, and its processes for identifying recipient governments and issuing licenses proved sufficiently complex – four years elapsed from adoption of the change in 2004 and delivery of the first shipment – that it was heavily criticized within Canada and also attracted little interest.³⁰

In September 2003 as prices continued to fall, the WHO began planning an ambitious “3 by 5” program with the goal of delivering ART to 3 million HIV-infected persons in developing countries within five years. The program would rely on a limited set of combination ART medications, chosen from among the formulations regarded as most effective in developing countries. Severe difficulties plagued the program from the start. WHO lacked staff capacity to evaluate generic versions of ART, so relied on national testing in the country of manufacture. However, the national testing was not always sufficient to assure the generic combinations were as effective as the patented combinations they reproduced. Problems with the list became public knowledge in May and August 2004 when WHO took some generic formulations made by Indian makers Cipla and Ranbaxy off the list because of questions about the adequacy of the testing.³¹ The rate at which WHO hoped to scale up treatment also exceeded the capacity of most of the national health services that would be providing the actual treatment. These concerns about program design and adequacy led both the Global Fund (which generally avoided funneling its aid through UN agencies) and PEPFAR to reject WHO requests for financial support. The Canadian International Development Agency offered funding on condition that there be an independent outside review of the program first. Even before the final review report, which was highly critical of the program's design and implementation, was issued in June 2006,³² the government of South Africa (which had not yet fully disavowed the extreme HIV denial that informed government policy starting in 1999³³), had already refused to participate in 3 by 5 and was keeping the WHO at arm's length.

In the meantime other international collaborations helping developing country health services build up their capacities to provide HIV treatment were underway through the Technological Network on HIV/AIDS, a cooperation among Brazil, China, Nigeria, Russia, and Ukraine and the International Treatment Preparedness Coalition, a program of technical cooperation among local NGOs and HIV treatment providers in developing countries managed and supported by the German Agency for Technical Cooperation.³⁴

³⁰ Lybecker and Fowler 2009, 222-39.

³¹ WHO. 2004. “Removal of antiretroviral products from WHO prequalification.” 11 Nov. 2004. Available at <http://www.who.int/hiv/topics/me/3by5evaluationreport.pdf> (accessed 2 April 2010).

³² Battistella Nemes and others. 2006. Evaluation of WHO's contribution to '3 by 5'." Available from <http://www.who.int/hiv/topics/me/3by5evaluationreport.pdf> (accessed 27 March 2010).

³³ Though President Mbeki had moderated his stance against ART therapy as unnecessary and harmful after 5000 medical scientists from around the world affirmed in the 2001 Durban Declaration that HIV is the cause of AIDS and ART the only effective treatment known, Health Minister Manto Tshabalala-Msimang was still advocating use of unproven folk remedies and inhibiting distribution of ART in early 2006. See the Editorial “Denying Science” in *Nature Medicine* 12 (4): 369 (April 2006).

³⁴ Noted briefly in Roger Bate and Lorraine Mooney. 2006. “WHO's comprehensive HIV treatment failure: Will we learn the real lessons from 3 by 5?” *American Enterprise Institute Working Paper* #133, p 10 (November 2006).

Round Two

By the time WHO ceased pursuing “3 by 5” in 2006, the second phase of the contention over HIV treatment prices was engaged. Again United Nations meetings strengthened the normative framework supporting claims that HIV treatments should be provided to all who need them regardless of ability to pay. The special meeting convened in September 2006 for a five-year follow-up on the 2001 Declaration of Commitment on HIV/AIDS issued a new Political Declaration on AIDS. The preamble repeated the human rights framing of the question, most directly in Paragraph 12:

12. Reaffirm[ing] also that access to medication in the context of pandemics, such as HIV/AIDS, is one of the fundamental elements to achieve progressively the full realization of the right of everyone to the enjoyment of the highest attainable standard of physical and mental health.

Paragraph 15 stated the implications for trade and other policies:

15. Recogniz[ing] further that to mount a comprehensive response, we must overcome any legal, regulatory, trade and other barriers that block access to prevention, treatment, care and support; commit adequate resources; promote and protect all human rights and fundamental freedoms for all; promote gender equality and empowerment of women; promote and protect the rights of the girl child in order to reduce the vulnerability of the girl child to HIV/AIDS; strengthen health systems and support health workers; support greater involvement of people living with HIV; scale up the use of known effective and comprehensive prevention interventions; do everything necessary to ensure access to life-saving drugs and prevention tools; and develop with equal urgency better tools – drugs, diagnostics and prevention technologies, including vaccines and microbicides – for the future;

The portion laying out policy commitments included several statements relating to drug patents and the need for continuing innovation reflecting compromises among various positions in the debates:

43. Reaffirm that the World Trade Organization’s Agreement on Trade-Related Aspects of Intellectual Property Rights does not and should not prevent members from taking measures now and in the future to protect public health. Accordingly, while reiterating our commitment to the TRIPS Agreement, [we] reaffirm that the Agreement can and should be interpreted and implemented in a manner supportive of the right to protect public health and, in particular, to promote access to medicines for all including the production of generic antiretroviral drugs and other essential drugs for AIDS-related infections. In this connection, we reaffirm the right to use, to the full, the provisions in the TRIPS Agreement, the Doha Declaration on the TRIPS Agreement and Public Health and the World Trade Organization’s General Council Decision of 2003 and amendments to Article 31, which provide flexibilities for this purpose;
44. Resolve to assist developing countries to enable them to employ the flexibilities outlined in the TRIPS Agreement, and to strengthen their capacities for this purpose;
45. Commit ourselves to intensifying investment in and efforts towards the research and development of new, safe and affordable HIV/AIDS-related medicines, products and technologies, such as vaccines, female-controlled methods and microbicides, pediatric antiretroviral formulations, including through such mechanisms as Advance Market

- Commitments, and to encouraging increased investment in HIV/AIDS-related research and development in traditional medicine;
46. Encourage pharmaceutical companies, donors, multilateral organizations and other partners to develop public-private partnerships in support of research and development and technology transfer, and in the comprehensive response to HIV/AIDS;
 47. Encourage bilateral, regional and international efforts to promote bulk procurement, price negotiations and licensing to lower prices for HIV prevention products, diagnostics, medicines and treatment commodities, while recognizing that intellectual property protection is important for the development of new medicines and recognizing the concerns about its effects on prices;³⁵

The second round of controversy over the prices of HIV treatments arise even though the prices of first-line treatments were continuing to decline because the various strains of the HIV virus were developing resistance to those treatments. To maintain their immune systems, an increasing number of HIV-infected individuals needed to start with or shift over to second-line treatments. These had been developed in the 1990s and were still under patent. Again the Brazilian government made the first moves because it had scaled up its provision of ART earlier than other developing countries, so was the first to face widespread need for second-line treatments. In 2005, Brazilian activists were claiming that the government was spending 80% of the National Aids Program budget allocation for ART on imported patented drugs. They further estimated that 70% of that spending was used to acquire sufficient doses of four medications: Kaletra (Abbott Laboratories's patented lopinavir/ritonavir combination), Viraid (Gilead's patented version of tenofovir), Sustiva (Merck's patented version of efavirenz), and Viracept (Hoffmann-LaRoche's patented version of nelfinavir).³⁶ Hence they advocated intensifying pressure on drug companies to reduce prices either through negotiations or through compulsory licensing. In June 2005 the Brazilian Chamber of Deputies (lower house of the national legislature) adopted a draft determination authorizing the government to issue compulsory licenses for local production of the lopinavir/ritonavir combination, tenofovir, and efavirenz. Lobbying by US-based pharmaceutical companies, induced a degree of caution in the government. However, it did continue to press for price reductions with considerable success. This pattern was broken in 2007 when negotiations with Merck over the price of Sustiva (efavirenz) reached an impasse. Merck was ready to reduce the price from \$1.57 a pill to \$1.10 a pill (from \$573 per patient per year to \$401 per patient per year), but the Brazilian government was hoping to get a price more like the \$0.65 a pill (\$237 per patient per year) paid by Thailand. Companies resisted because Brazil, was an upper middle income country in the World Bank classifications and Thailand a lower middle income country. The Brazilian government was so keenly interested in Sustiva because it is a "once a day" pill more effective than most other non-nucleoside reverse transcriptase inhibitors. Activists estimated that purchases at the Thai price rather than the \$1.10 per pill Merck was offering would save the Brazilian

³⁵ UN General Assembly Resolution 60/262, Political Declaration on HIV/AIDS, adopted on 2 June 2006. The full text is available at <http://daccess-dds-ny.un.org/doc/UNDOC/GEN/N05/503/32/PDF/N0550332.pdf?OpenElement> (accessed 2 April 2010), and is also included in appendix B.

³⁶ Estimates quoted in Weissman, "Big pharma and AIDS," p. 15.

government \$30 million in 2007 alone and a total of \$237 million by the time Merck's patent expired in 2012.³⁷

These contentions between the Brazilian government and pharmaceutical firms only cover government purchases of HIV treatments. The government exerts control over prices charged to private buyers through its Chamber for the Regulation of the Market of Medicines, which must approve the price before a drug can be sold in Brazil. Firms can petition for later adjustments, which the Chamber reviews once a year.³⁸

The military government that ruled Thailand from September 2006 through January 2008 and its civilian successor went further. The military government began in November 2006 by issuing a compulsory license for production of Sustiva (efavirenz). In January 2007 it issued a compulsory license on Kaletra (lopinavir/ritonavir combination) and on the heart drug clopidogrel. Aware that the US pharmaceutical firms were likely to seek US government support for trade countermeasures, the Thai government issued a 100 page explanation of its actions. This did not prevent the Office of US Trade Representative from placing Thailand on its "priority watch list" of countries likely to ignore intellectual property rights, but did impress activists with the Thai government's openness and good faith in issuing the licenses. US-based activists persuaded 22 members of the US Congress to publicly question the USTR's actions. In January 2008, the Thai government also issued compulsory licenses covering three non-HIV drugs letrozole (a breast cancer treatment patented by Novartis), docetaxel (a breast and lung cancer treatment patented by Sanofi-Aventis) and erlotinib (a lung, pancreatic and ovarian cancer treatment patented by Hoffmann-LaRoche). On taking power the new civilian government stated that it would review the compulsory licenses, but in the end decided to maintain the licenses while confirming that the Minister of Commerce holds the authority to end them.

The major drug companies accepted that governments wanted assured access to antiretroviral therapies at low prices, and were accustomed to seeing some price negotiations end with the government issuing a compulsory license, but they strongly resisted the Thai move to start local production of the heart and cancer drugs. Though health access activists hailed the decision as a great victory, and pressured Novartis to drop its efforts to defend its letrozole patent, the Thai choices drew attention to the potential for using claims about rights to "essential medicines" or the need to secure "treatments addressing global pandemics" for medications treating other diseases. While HIV treatments tenofovir, lopinavir/ritonavir and efavirenz are included on the WHO list of "essential medicines," letrozole, docataxel, and erlinotab are not on that list.³⁹

The companies affected by the compulsory licenses on heart and cancer drugs feared that other governments would emulate Thailand's expanded practices and reacted very strongly. They not only continued their lobbying of the Bush administration in the United States to threaten trade retaliation; they also decided to limit their dealings in Thailand by withdrawing other drugs from that country's market. The

³⁷ "Market Watch: Pharmaceuticals" and Bloomberg report available at <http://www.bloomberg.com/apps/news?pid=20601087&sid=a6sFuqDEGDKU> (accessed 27 March 2010).

³⁸ Deborah Portillo and Rana Gosain. 2007. "IP Focus Americas: Drugs dispute demands action," *Managing Intellectual Property*, October 2007, pp. 27-30.

³⁹WHO List of Essential Medicines at http://www.who.int/medicines/publications/essentialmedicines/Updated_sixteenth_adult_list_en.pdf (accessed 27 March 2010).

notion that Thai ideas might catch on elsewhere received some credence from a June 2009 speech by Venezuelan President Hugo Chavez. In the course of a dispute over prices with some US-based firms, he stated that "A song is intellectual property, but an invention or a scientific discovery should be knowledge for the world, especially medicine."⁴⁰

The new leftist government in Ecuador also took aim at drug patents with a presidential decree establishing procedures for granting compulsory licenses and issuing one for importation of a generic version of the Ritonavir/Lopinavir combination. In a discussion in the WTO's TRIPS Council, which addresses intellectual property rights issues, the Egyptian representative expressed a hope this would help dissipate "the stigma" attached to compulsory licensing.⁴¹

Besides threats or actual uses of compulsory licensing, the second round of controversy over patents has also included a good deal of effort to limit the number patents and the scope of patent protection by defining the "novelty" required for a patent in demanding terms. This is another area of what trade lawyers call "flexibilities" in the TRIPS Agreement because the Agreement does not define the degree of novelty required for issuing a patent. Each country can decide this question on its own.

Local AIDS and health activists, social movements advocating for the poor, and the generics-based segment of the Indian pharmaceutical industry showed lively interest in these possibilities as India's patent law was revised in preparation for coming into compliance with the TRIPS Agreement. After considerable debate, the Patent (Amendments) Act 2005⁴² included provisions:

- a. allowing citizens, associations, and firms to object to patent applications before the Patent Office has issued a patent and to petition for its revocation after a patent has been issued;
- b. allowing revocation of a patent when revocation is "in the public interest;"
- c. limiting patents to new products, thus excluding attempts to "evergreen" a patent by securing separate patents on new uses of a previously-patented product; and
- d. including in the definition of "novelty" a requirement that the advance be "non-obvious"

The first challenge to a drug patent application under the new Indian law was filed in 2005 by the Cancer Patients Aid Association against Novartis' application for a patent on Glivec, its brand name for imatinib mesylate, a very effective leukemia treatment. The Cancer Patients Aid Association argued that this application did not qualify for a patent because imatinib mesylate was merely another form of an already-known substance, imatinib, that Novartis had already patented in 1993. In 2006 the Patent Office rejected Novartis' patent application, and Novartis appealed to the courts. Novartis' lawyers framed their appeal as

⁴⁰ As reported by Reuters, June 21, 2009. See <http://www.reuters.com/article/idUSN2148323120090621> (accessed 27 March 2010).

⁴¹ TRIPS: Council debates anti-counterfeiting talks, patents on life, WTO News Items http://www.wto.org/english/news_e/news10_e/trip_08jun10_e.htm

⁴² The Patents (Amendment) Act. *The Gazette of India* Extraordinary, 5 April 2005. Available at http://ipindia.nic.oin/ipr/patent/patent_2005.pdf.

an argument that the rejection should not stand because Indian patent law had a more restrictive definition of novelty than allowed under the TRIPS agreement. Activists regarded the appeal as a challenge to the new Patent Law as a whole and organized a global campaign to pressure Novartis into dropping its appeal. Novartis persisted, only to have the court rule that any claim that national law is incompatible with TRIPS has to be settled in the WTO dispute-settlement process (an inter-state process not open to private firms), not in national courts. Though the ruling side-stepped rather than addressed the substance of Novartis' claim, it left the rejection in place. Activists perceived the ruling as putting "patients before patents" and prepared to file more objections to other patents.⁴³

Tibotec Pharmaceuticals' protease inhibitor Darunavir (DRV) and Gilead Science's Tenofovir came under close scrutiny when the companies filed for drug registration and patent protection in India in 2009. Tibotec had already made arrangements for royalty-free production of Darunavir by Indian generics maker Emcure when it submitted its applications. As Indian authorities considered the applications, both drugs were the subject of much anticipation. It was widely known that Darunavir taken either alone or with Ritonavir was as effective as other treatments in adults whose HIV viral loads were already suppressed by drug treatment and appeared to inspire HIV mutations. Tenofovir has also proven more effective than earlier therapies. Though both companies argued their drugs deserved patent protection under the 2005 Act criterion of showing enhanced efficiency, Indian activists and Indian generics drug maker Cipla filed petitions challenging that claim. The Indian Patent Office rejected Tibotec's and Gilead's applications and Indian courts upheld that rejection in September 2009.

Activists were very happy with the decision, maintaining that the denial of patent protection would help "save countless lives in the developing world."⁴⁴ Some observers worried that the question might be reopened if the Indian Supreme Court ruled in favor of Novartis in its appeal of decision against granting it a patent on Glivec, but health policy makers moved ahead. Health ministries in a number of developing countries that had been holding back added Darunavir and Tenofovir to their sets of HIV treatments because the rejection meant that Indian generics houses would be able to export the drug without any restrictions.⁴⁵

Impact on Prices and Distribution

Campaigns to force down the prices charged for the drugs used in antiretroviral treatment have gained notable successes. In early summer 2007 the Clinton Foundation was able to secure a "once a day" pill combining tenofovir, efavirenz, and lamivudine from Indian generics makers Cipla and Matrix for somewhat less than \$365 per person per year. This was more expensive than the \$99 per person per year for which it

⁴³ Weissman, "Big pharma" pp. 13-15 and Ruth David 2007. "Novartis Set Back In India Patent Fight Over Glivec." *Forbes*. Aug. 7, 2007. Available at http://www.forbes.com/2007/08/07/novartis-glivec-generics-markets-equity-cx_rd_0807markets02.html (accessed 2 April 2010).

⁴⁴ James Kamau of the Kenya Treatment Access Movement quoted by IRIN/PlusNews. Story posted at <http://www.iasociety.org/Default.aspx?pagelD=5&elementId=12143>

⁴⁵ Khomba Singh. 2009. "US's Gilead appeals against patent rejection of AIDS drug Viread." *The Economic Times*. 8 Dec. 2009, available at <http://economictimes.indiatimes.com/news/news-by-industry/healthcare/biotech/pharmaceuticals/US-Gilead-appeals-against-patent-rejection-of-AIDS-drug-Viread/articleshow/5312342.cms>. Also noted at <http://www.iasociety.org/Default.aspx?pagelD=5&elementId=12143>.

could buy first-line combinations, but comparable to the prices of first-line ARTs when they were introduced in the mid 1990s. Also in 2007, the lowest price for a generic version of heat-stable lopinavir/ritonavir was \$695 per person per year. This was higher than the price patent-holder Abbott Laboratories charged governments of least developed countries for its Kaletra brand, but lower than what it charged governments of middle income countries.⁴⁶

Efforts to assess the prevalence of HIV/AIDS and the proportion of HIV-infected persons receiving antiretroviral treatment remain plagued by large amounts of uncertainty. Social stigmas attached to HIV and AIDS in many countries discourage the infected from getting tested or securing treatment. The costs of tests and availability of clinics create other barriers unaffected by lowering prices of HIV drugs. Continuing lack of a vaccine or a cure for HIV means that how much the need for antiretroviral treatment increases depends on the success of efforts to contain the pandemic. So far, containment efforts have varying degrees of success. The spread has been less extensive in Asia than in Africa; in developed countries the spread is limited to those engaged in the most risky behaviors. The joint UN Program on AIDS estimated in 2009 that 4 million persons worldwide were receiving ART, 6 million fewer than the 10 million estimated to need treatment. More discouragingly is also estimated that the number of new infections around the world was 35% higher than the number of HIV-related deaths.⁴⁷ Thus the total of persons needing ART continues to rise. Wherever spread continues, the scale of the pandemic is creating huge needs that are limiting what governments can do to address other health issues.⁴⁸

However the basic humanitarian claim that life-saving treatments should be available for all who need them will not fade. Values of human rights, community, and human solidarity, though based on different ethical principles and justifications, combine to give humanitarian appeals strong pull in most societies. While the continuing debate about the efficacy of promoting innovation through systems of intellectual property rights usually rests on differing conclusions regarding what is economically optimal, creation and maintenance of intellectual property rights – including patents -- in areas of technology applied to fulfilling basic human needs will also be assessed on ethical grounds.⁴⁹

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⁴⁶Weissman, "Big pharma" p. 21.

⁴⁷ Estimate quoted in Princeton N. Lyman and Stephen B. Wittels. 2010. "No good deed goes unpunished: The unintended consequences of Washington's HIV/AIDS programs." *Foreign Affairs* 89 (4): 74-84 (July/August).

⁴⁸ See Lyman and Wittels 2010.

⁴⁹ Humanitarian concern about the lack of drug development relevant to diseases endemic in many developing countries has led to some interesting industry-foundation initiatives, such as the Wellcome Trust-Merck joint establishment of the Hilleman Laboratories in India to pursue research and development of drugs and vaccines designed for developing country conditions (see <http://www.hillemanlaboratories.in/news/>) and GlaxoSmithKline's "Open Lab" opening up company databases and places in one of the company's own labs for medical scientists working on drugs that will be used against major diseases in developing countries (see January 2010 press release available at www.gsk.com).