

Sustaining access to antiretroviral therapy in developing countries: lessons from Brazil and Thailand

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Antiretroviral rollout in Brazil and Thailand Brazil and Thailand are among few developing countries to achieve universal access to antiretroviral therapy. Three factors were critical to this success: legislation for free access to treatment; public sector capacity to manufacture medicines; and strong civil society action to support government initiatives to improve access.

Local production of affordable, non-patented drugs Many older antiretroviral drugs are not patented in either country and affordable generic versions are manufactured by local pharmaceutical institutes.

Efforts to ensure access to expensive, patented drugs Developing countries were not required to grant patents on medicines until 2005, but under US government threats of trade sanctions, Thailand and Brazil began doing so at least ten years prior to this date. Brazil has used price negotiations with multi-national pharmaceutical companies to lower the price of newer patented antiretrovirals. However, the prices obtained by this approach remain unaffordable. Thailand recently employed compulsory licensing for two antiretrovirals, obtaining substantial price reductions, both for generic and brand products. Following Thailand's example, Brazil has issued its first compulsory license.

Lessons learned Middle-income countries are unable to pay the high prices of multinational pharmaceutical companies. By relying on negotiations with companies, Brazil pays up to four times more for some drugs compared with prices available internationally. Compulsory licensing has brought treatment with newer antiretrovirals within reach in Thailand, but has resulted in pressure from industry and the US government. An informed and engaged civil society is essential to support governments in putting health before trade.

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Introduction

Increasing and sustaining access to affordable antiretroviral therapy (ART) continues to pose many challenges for the developing world. Brazil and Thailand are among the few developing countries that can be said to have achieved universal access to ART [1]. The success of these two countries has depended on three positive factors: a commitment to ensuring universal access to ART with legislation giving free access to treatment; public sector capacity to manufacture medicines; and strong civil society action to challenge the lack of access to medicines

and support government initiatives to improve access. This paper looks at strategies employed to improve access to key antiretroviral drugs in these two countries and reflects on the relative successes of each in order to identify factors for future success.

Antiretroviral rollout

The Brazilian public health system began providing antiretroviral agents (zidovudine monotherapy) in 1991.

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Table 1. Demographics, development status and HIV in Brazil and Thailand.

	Brazil	Thailand
Population	186.8 million	60.1 million
Human development index	69	74
GDP per capita	US\$8195	US\$8090
HIV prevalence (adults)	0.61% ^a	1%
No. of people living with HIV/AIDS (December 2006)	620 000	580 000
No. on ART	175 000 (August, 2006)	83 000 (December 2006)

ART, Antiretroviral therapy; GDP, gross domestic product. Sources: UNDP [11], Brazilian Ministry of Health, Thai Bureau of AIDS, TB and STI, Ministry of Public Health.

^aEstimates for 15–49 year olds for 2004 [11–13].

At that time, new medicines were being clinically approved internationally and civil society groups, which have played a central role in Brazil's response to AIDS [2], started to take legal action demanding that the government supply these new drugs. This approach established the judicial basis for guaranteeing universal access to treatment for people living with HIV/AIDS within the federal constitutional right to health [3].

Nationwide access to ART was kick-started in 1996 when Brazil's Congress enacted a law requiring free treatment for individuals with AIDS. Under this law, responsibility to provide ART came under the federal government [4]. By the end of 1997, an estimated 35 900 people were receiving ART; this increased to 105 000 by 2001 and 153 000 by the end of 2004 [5]. Between 1996 and 2004 AIDS mortality was reduced by 50%, and AIDS-related hospitalizations fell by 80% [6].

Thailand began providing antiretroviral monotherapy with zidovudine in 1992, switching to dual therapy (zidovudine with either didanosine or zalcitabine) in 1995. Zidovudine became available generically in 1995, but didanosine and zalcitabine were patented and expensive. A joint evaluation by the World Bank, the World Health Organization (WHO) and the Ministry of Public Health (MOPH) concluded that the programme was high cost and low benefit [7,8], but this economic review did not take into account the possibility of lower drug prices. In 2000, the government began providing triple therapy for individuals with HIV/AIDS, but again reliance on expensive brand drugs limited the beneficiaries to 1500 individuals.

The wide-scale provision of ART began in 2003, once government-produced generic antiretroviral drugs became broadly available, in particular the fixed-dose triple combination of stavudine, lamivudine and nevirapine (GPO-vir). In February 2003, a delegation of senior officials from MOPH and individuals living with HIV/AIDS from Thailand undertook a study visit to Brazil. This exchange, which was supported by UNAIDS,

WHO, Médecins Sans Frontières and Oxfam, helped strengthen Thailand's newly established national HIV/AIDS treatment programme and supported Thailand's efforts to manufacture and procure generic antiretroviral medicines [9]. Since then, the number of individuals on ART has increased sharply from approximately 3000 at the start of 2002 to 27 000 by the end of 2003, rising to 53 000 by February 2005 [10] and 83 000 by December 2006 (see Table 1).

Generic production and treatment costs

In both countries the local generic production of antiretroviral drugs by private (national) and state-owned pharmaceutical institutes has been essential to ensuring affordable prices for ART [14].

In Brazil, generic antiretroviral drugs are produced by a number of federal and state laboratories, the most significant being the federal public laboratory Far-Manguinhos. Local production of non-patented first-line drugs, coupled with price negotiations with pharmaceutical companies for newer drugs subject to patent, has helped the government steadily to reduce its average annual cost for ART, from approximately US\$4350 per patient in 1999 to US\$1517 in 2004 [15]. (Unless otherwise stated, all prices in this article are public sector prices.) Eight of the 17 antiretroviral drugs currently purchased by the government are manufactured domestically.

Thailand's Government Pharmaceutical Organization (GPO) began research and development into antiretroviral drugs (zidovudine and didanosine) in 1992. Generic zidovudine entered the market in 1995 at one-sixth the price of the originator drug. Generic didanosine was blocked in 1998 by a patent application by BMS (Bristol-Myers Squibb) [16]. GPO currently produces six antiretroviral drugs and two fixed-dose combinations in a range of dosages, which are between two (for nevirapine) and 25 (for stavudine) times cheaper than the cheapest originator equivalents. Triple therapy is currently available as a fixed-dose combination (GPO-vir) at a monthly cost of US\$360 per patient per year, compared with US\$4376 for the patented, non-fixed-dose combination drugs.

The average cost of treatment in both countries is increasing as a result of the increasing need to access newer, patented medicines.

Rising intellectual property protection

Local antiretroviral manufacture in Brazil and Thailand has depended on the fact that these medicines were not patented in both countries. According to the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), developing

Table 2. Key legal provisions improving or limiting access to medicines in Brazil and Thailand.

Legal provision	Description	Purpose	Practical implications		Examples	
			Brazil	Thailand	Brazil	Thailand
Improves access to medicines						
Compulsory licensing	Authorization given by a judicial or administrative authority to a third party for the use of a patented invention, without the consent of the patent holder	To allow governments to override patents whenever needed, for example in the interests of public health	Has been used as a 'credible threat' in price negotiations with patent holders	Civil society has pushed for compulsory licenses since 1998. First licenses issued in 2006 and 2007	Efavirenz	Efavirenz, lopinavir/ritonavir, clopidogrel
Pre-grant opposition	Provide the National Patent Office with technical information about the patentability of filed claims while the patent is under analysis	To avoid the granting of a patent when it does not fulfill patentability requirements.	Very little use so far. Two oppositions on AIDS drugs filed by public laboratory on one hand and by civil society on the other. Total lack of transparency to monitor the patent analysis process	Interested parties, such as Thai GPO or other institutions, have opposed the granting of patents that they deem unjustified.	Second patent claim for lopinavir/ritonavir. Tenofovir patent claim	Zidovudine/lamivudine (see Table 3)
Prior consent of Ministry of Health – Brazil only	Health ministry participation (through the DRA) in analysing pharmaceutical patent claims [18]	To avoid unjustified exclusivity rights [19] that may have an impact on public health [20]	Frivolous patents rejected and evergreening possibilities blocked. Strong Pharma pressures to withdraw this provision has caused (still ongoing) intragovernmental body disputes still undergoing. Many patent applications are pending because of opposite views between patent office and DRA	–	Valgancyclovir (for treatment of cytomegalovirus infection). DRA rejected patent application on the grounds of lack of novelty and inventiveness. Roche filed a federal lawsuit arguing that the DRA had no legitimacy to interfere in patent applications [19]. Case ongoing	
Limits access to medicines						
Amendments to national patent law resulting in implementation of TRIPS earlier than required by WTO agreements	National legislation compliant with TRIPS earlier than required by WTO (2005)	To limit the scope of generic production	Generic production restricted earlier than necessary and reduction of local production on newer drugs	Generic production restricted earlier than necessary	The legislation was changed in 1996 and pharmaceutical patents started to be granted in 1997 retroactively	TRIPS compliant legislation introduced in 1998
SMP (a form of pipeline protection)	A period (2–5 years) of market exclusivity awarded to companies when registering originator brand pharmaceutical products, irrespective of whether the product is under patent	To enable collection of data on drug safety	–	In practice, little safety data are collected. Generic production of non-patented medicines is held back for 2–5 years	–	Fluconazole (for treatment of Cryptococcosis and other fungal infections) has never been patented in Thailand but remained a monopoly product between 1992 and 1998 through SMP protection. After it was released from SMP, the price fell to 5% of the originator price within 6 months [21] Tenofovir is not patented in Thailand but will remain a monopoly product until release from SMP (August 2008 at the earliest)
Pipeline mechanism	Retroactive protection allowing pharmaceuticals already patented in other countries to be patented in Brazil even if priority date precedes 1995 [22]	To widen Pharma's patent protection above the TRIPS requirement for drugs that have lost their novelty requirements at the time of TRIPS implementation	Patent protection of medicines crucial for public health without analysis of patentability requirement in Brazil	–	To treat HIV/AIDS: abacavir, efavirenz, lopinavir/ritonavir, nelfinavir, amprenavir. To treat cancer: imatinib mesilate (brand name Gleevec)	–

DRA, drug regulator agency; GPO, Government Pharmaceutical Organization; SMP, safety monitoring programme; TRIPS, Trade-Related Aspects of Intellectual Property Rights; WTO, World Trade Organization.

countries were not required to grant patents on medicines until January 2005 [17]. Trade pressure, however, particularly from the United States, pushed this forward in both countries, and the TRIPS Agreement was fully implemented in Brazil in 1997 and in Thailand in 1992 (Table 2) [10,18–22].

Up until the early 1980s, Brazil's intellectual property laws did not recognize patents to pharmaceutical products and processes. In response to US pressure, however, including economic sanctions, the Brazilian government passed an industrial property law [23], which was approved in 1996, the same year as the law guaranteeing free AIDS treatment [24]. The new patent law included a number of provisions that go further than required by the TRIPS Agreement (TRIPS-plus provisions). The most detrimental of these to the availability of antiretroviral medicines is the 'pipeline mechanism', which provides retroactive patent protection for medicines not yet marketed in Brazil but which have been granted patent protection elsewhere. Under this mechanism, a number of key antiretroviral drugs, including abacavir, efavirenz, lopinavir/ritonavir, nelfinavir and amprenavir were granted patent protection without any technical examination in Brazil [25,26].

As a result of concern over rising intellectual property protection, an amendment was passed in 2001 that included a number of public health flexibilities. One such mechanism, called 'prior consent', authorizes the Brazilian Drug Regulatory Authority to assess patent claims for pharmaceutical products and processes before a patent is granted [18]. This is a rare example of a government health authority playing a formal role in the examination of pharmaceutical patent applications.

Thailand has been under threat of trade sanctions from the US government to introduce strong patent protection for pharmaceuticals since 1985, even though process patents for pharmaceuticals had been introduced in the Thai Patent Act since 1979 [27–29]. Out of concern for public health, Thai academics, lawyers, non-governmental organizations and health advocates formed an alliance to monitor this trade pressure, but public awareness remained low, and despite the efforts of civil society intellectual property protection has increased. In 1992, under US government pressure [30], Thailand passed a law introducing pharmaceutical product patent protection and extending patent life from 15 to 20 years. In addition, 'pipeline product protection' was introduced to provide market exclusivity for new drugs registered in Thailand that had been granted a patent elsewhere between 1986 and 1991. The provision, known as the 'Safety Monitoring Programme' allows a period of 2 years' market exclusivity (renewable on request of the pharmaceutical company) for the purposes of collecting postmarketing surveillance data (Table 2). As a safeguard, the government created the Pharmaceutical Patent

Review Board, with authority to collect economic data, including the production cost of pharmaceuticals, but the United States objected [31], and after a 1999 amendment to the Thai Patent Act the Pharmaceutical Patent Review Board was disbanded and the right to issue compulsory licences for pharmaceuticals was restricted [32]. The Safety Monitoring Programme remains in place.

Rising drug prices

All HIV/AIDS treatment programmes need access to newer medicines to provide treatment options in case of drug resistance or intolerance, and the need for these medicines increases over time. These newer drugs are under patent protection in the majority of countries and are far more expensive than those used in first-line [33].

Brazil started to grant patents for pharmaceuticals in May 1997. Within a year, new patented medicines were included in the national AIDS programme, and these began to consume an increasing amount of the treatment budget [14]. By 2003, three newer patented drugs, lopinavir/ritonavir, nelfinavir, and efavirenz, were taking up 63% of the total ART budget. In 2005, imports accounted for 80% of government expenditures on antiretroviral drugs, and total annual expenditures are projected to increase further with the inclusion of newer drugs such as atazanavir (US\$2190 per patient/year) and emtricitabine (US\$17 000 per patient/year) in the national treatment protocol [6].

In Thailand, antiretroviral expenditure as a percentage of the national health budget is expected to increase from 6.1% in 2004 to 10.2% in 2010. According to WHO estimates, second-line therapy for one quarter of all patients will be absorbing three-quarters of the treatment budget by 2020, and the cost of ART with second-line regimens could reach US\$500 million per year if prices remain at current levels [34].

Efforts to ensure access to key antiretroviral drugs

Civil society and government in both countries have fought hard to secure the availability of antiretroviral drugs, using a range of strategies and policy options to challenge and override patents (Table 3).

Negotiation and compromise in Brazil

In Brazil, price negotiations, backed by the threat of compulsory licensing and local generic production, have been the main strategy used by the government to lower the price of patented antiretroviral drugs.

Between 2001 and 2003 the Brazilian government negotiated discounts on a number of patented drugs.

Table 3. Overview of strategies to improve access to affordable medicines in Brazil and Thailand.

Policy approach	Drug	Action taken by	Outcome	Consequence
Negotiations with pharmaceutical companies	Efavirenz	MOPH, Thailand, 2001	Merck offers price of US\$500	High price and continued supply problems; compulsory license pursued
	Tenofovir Lopinavir/ritonavir	MOH, Brazil, 2003	Merck offers price of US\$760	Government accepts price
		MOPH, Thailand, 2001	Gilead offers price of US\$360	Gilead price accepted
	Challenge to patent application (pre-grant opposition)	Nelfinavir Nelfinavir 625 mg tablets	Civil society and government, Thailand, 2006	Abbott offers price of US\$2200
MOH, Brazil, 2003			Abbott offers price of US\$3241	Government accepts price
GPO, Thailand, 2005		Roche offers price of US\$31 718	Government accepts price	
Challenge to existing patent Compulsory licence Threatened	Nevirapine syrup	GPO, Thailand, 2006	Rejected: GPO appealed in November 2006	Decision pending
	Zidovudine/ lamivudine	Health and Development Foundation, Thailand, 2006	Successful: application withdrawn	Generic production and lower price maintained
	Didanosine	Civil society, Thailand, 2002	Patent overturned in 2004	Generic production started by GPO
Issued	Lopinavir/ritonavir	MOPH, Brazil, 2006	Roche offers lower price; government drops compulsory licensing	Price fixed at US\$1380 until 2011. Civil society file a civil action lawsuit
	Efavirenz	MOPH, Thailand, 2006	Compulsory license issued despite objections from Merck and the US government. Abbott offers price of US\$2000	Generic efavirenz to be imported from India at US\$224; local production initiated
	Lopinavir/ritonavir	MOPH, Thailand, 2007	Abbott offers a price of \$US1000 but threatens to withhold all new medicines unless compulsory licensing is dropped	Government continues with compulsory licensing for generic version costing US\$676
	Efavirenz	MOPH, Brazil, 2007		Generic to be imported (price \$170), while local production is prepared

GPO, Government Pharmaceutical Organization; MOH, Ministry of Health; MOPH, Ministry of Public Health; WHO, World Health Organization.

By basing negotiations on production cost estimates calculated by FarManguinhos [35] and threats to issue a compulsory licence, significant price reductions were obtained for efavirenz (73%), lopinavir/ritonavir (56%) and nelfinavir (74%). Although these percentage discounts appear impressive, the initial prices offered by pharmaceutical companies were very high (comparable to US prices) and the discounted prices obtained were still far higher than the best prices available internationally. From 2003 onwards, the price of most patented antiretroviral drugs in Brazil fell only marginally (Table 4). It was becoming clear that the government's negotiating

tactic of threatening to issue compulsory licences, without ever doing so, was losing credibility.

With increasing numbers of patients on second-line treatments, the average treatment cost had risen by over US\$1000 per patient per year to US\$2616 by 2005; the most expensive second-line drug, lopinavir/ritonavir, cost US\$3241 per patient per year.

In June 2005, the Brazilian government took a first step towards issuing a compulsory licence for lopinavir/ritonavir, announcing, in accordance with Brazilian law

Table 4. Best price of key antiretroviral drugs in Brazil and internationally.

	2003			2006		
	Government price (US\$)	Best international price (US\$)	Difference	Government price (US\$)	Best international price (US\$)	Difference
Efavirenz	580	438	× 1.3	580	220	× 2.6
Lopinavir/ritonavir	3241	500	× 6.5	1380	338	× 4.1
Nelfinavir	1718	880	× 2.0	1537	683	× 2.3
Tenofovir	2905	500	× 5.8	1382	500	× 2.8

[36], that this was in the public interest to sustain the HIV/AIDS treatment programme. At the same time, the government gave the patent holder, Abbott, 10 days to offer a reasonable price, but in fact negotiations were protracted over 4 months, and concluded with the government agreeing on a price of US\$1380 per patient per year for the old version and US\$1518 for the heat-stable version. The discounted price obtained was still far higher than the best prices available internationally by Abbott (US\$500 per patient/year), and production cost estimates published by the WHO (US\$338 per patient/year) [37]. In addition, the Brazilian government made a number of concessions demanded by Abbott, including restricting the use of the compulsory licence, and a moratorium on future price negotiations until 2011 [38].

In December 2005, these concessions forced civil society groups (GTPI/REBRIP) together with the public attorney's office to file a civil action lawsuit against both the Brazilian government and Abbott, demanding the use of compulsory licensing for lopinavir/ritonavir. The judges have so far prevented the case from moving forward, arguing that a compulsory licence would probably result in trade retaliation from the United States while Brazil does not have capacity for local production. This is currently being challenged on the grounds that several laboratories (state-owned and private) do in fact have sufficient production capacity [25,38].

Brazil finally issued its first compulsory licence for an antiretroviral drug in May 2007 for the drug efavirenz, currently used by 75 000 patients in Brazil [39]. This followed recent negotiations with the patent holder, Merck, which was only willing to offer a 2% discount on the current price (US\$580 per patient/year), more than twice the price offered to Thailand (US\$244) after the Thai government issued a compulsory licence (see below). A generic version will be bought from India at less than US\$170 in a first stage, pending local production by public a laboratory. This move, which was forcefully opposed by Merck, represents an important change in Brazil's previous strategy of accepting industry concessions without taking further action.

Challenging patents in Thailand

In Thailand, direct negotiations with pharmaceutical companies have had mixed success (Table 3). Reducing the cost of antiretroviral drugs has focused on two strategies: patent challenges and compulsory licensing.

The first successful challenge to an antiretroviral patent was made by civil society groups against a patent for didanosine. In May 2001, two patients and an AIDS non-governmental organization filed a lawsuit against Bristol-Myers Squibb, claiming that the patent application was invalid because details of the patent had been unlawfully altered (a dose restriction in the original patent application was altered), extending the patent protection beyond

the scope of the original patent application [16]. Bristol-Myers Squibb objected that patients had no legal right to challenge patents, but the court ruled that because pharmaceutical patents can lead to high prices and limit access to medicines, patients are injured by them and can challenge their legality. This ruling has important consequences internationally, as similar cases in other countries had been thrown out on this basis. Moreover, the court eventually found in favour of the plaintiffs, opening the way for generic production. This court case strengthened the confidence of people with HIV/AIDS in fighting for access to medicines, although the direct impact in terms of access to antiretroviral drugs in Thailand was limited because by the time the legal challenge had completed its course, standard national ART regimens had been set and did not include didanosine.

In early 2006, the Health and Development Foundation of Thailand filed a legal challenge against GlaxoSmith-Kline (GSK)'s application for a patent on the zidovudine/lamivudine fixed-dose combination on the grounds of 'nothing new', arguing that the combining of two known drugs, neither of which were patented in Thailand, could not be considered sufficiently inventive to merit a patent. The cost implications of a patent would have been significant: zidovudine/lamivudine has been produced generically by the Thai GPO since 2003 at a sales price of approximately US\$276 per patient per year; the originator equivalent sales price was US\$2436 per patient per year. The same legal challenge had been filed by civil society groups in India, and activists in both countries co-ordinated their campaigns. In August 2006, several hundred HIV-positive individuals demonstrated outside GSK's offices in Bangkok and Bangalore [40]. GSK withdrew the patent application in both countries the following day, and announced that it would also withdraw applications or granted patents for this formulation in all other countries [41]. Despite this promise, however, GSK continues to seek a patent for zidovudine/lamivudine in China.

Compulsory licensing for government (non-commercial) use has recently been employed in Thailand. The first example was for efavirenz. Since 2004, supply problems had resulted in stock-outs at several hospitals. Cost was also limiting access: Merck was charging over double (US\$468 per patient/year) the price available from Indian generics (US\$216 per patient/year), and the MOPH budget was only able to cover two-thirds of the need. Following failed negotiations with Merck for a lower price, the Thai Minister of Public Health announced in November 2006 that a compulsory licence would be issued for efavirenz, a move strongly supported by civil society groups [41]. Merck responded by offering a price of US\$288 per patient per year, but at the same time lobbied the US government and the Director General of the WHO [42] to pressure the Thai government to negotiate with Merck rather than issue a compulsory

licence [43]. Despite this pressure, the Thai government has followed through with the compulsory licence, and the first supply of generic efavirenz arrived in Thailand in February 2007.

Compulsory licences were issued for two more drugs in early 2007, clopidogrel (for heart disease), and the antiretroviral drug lopinavir/ritonavir [44]. The latter followed fruitless negotiations with the manufacturer, Abbott Laboratories, between 2004 and 2006 [45].

Until 2006, the best price Abbott had offered the Thai government was US\$2967 per patient per year [46]. Under global pressure from activist groups, Abbott announced in early 2006 a price of US\$500 per year for least developed countries, but excluding middle countries such as Brazil and Thailand [47]. Following continued pressure, Abbott announced a price of US\$2200 per patient per year for a list of countries defined by the company as 'middle-income' countries. This is, however, more than six times the current cost of first-line ART, and far too expensive for a country such as Thailand, where the average annual wage is US\$1600 per year.

At the end of January 2007, the Thai MOPH took steps to issue a government use compulsory licence for lopinavir/ritonavir [48]. Abbott responded by offering a price of US\$2000 per patient per year (at the time a generic company was offering \$1333 per patient/year). Given that the drug costs less than US\$400 to manufacture [37] the MOPH proceeded with the compulsory licence. The company discounted the price again, to US\$1000 per patient per year for both the old and the new version of the drug, and this offer was made available to 40 'middle-income' countries including Brazil.

At the same time, however, Abbott undertook an aggressive lobbying campaign to block the compulsory licensing. They announced that they would withhold registration of all new medicines from Thailand, stating that 'Thailand has chosen to break patents on numerous medicines, ignoring the patent system. As such, we've elected not to introduce new medicines there'. This was despite the fact that the WHO and several governments have confirmed that Thailand's actions are fully compliant with international law [49]. Abbott also mounted a misinformation campaign to spread false information about Thailand's compulsory licensing process, and requested that the US government pressure Thailand for allegedly 'stealing' their intellectual property; in response, the US government downgraded Thailand's trade status to a country with poor intellectual property protection. Civil society groups responded by demanding that the Thai Foreign Affairs and Commerce Ministries support the action of the Public Health Minister more actively [50].

In May 2007, a price of US\$676 per patient per year for generic heat-stable lopinavir/ritonavir was announced,

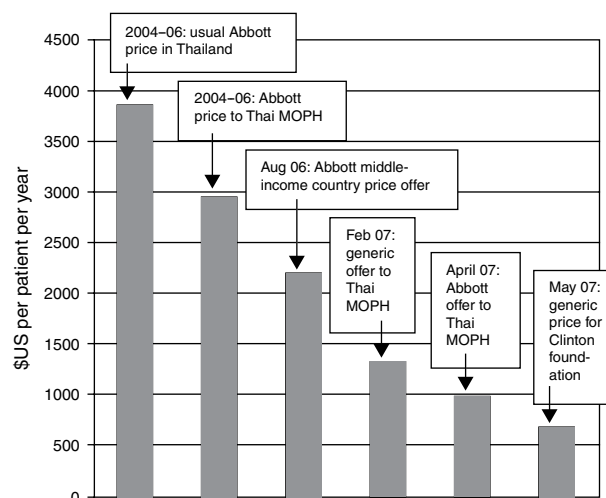


Fig. 1. Prices for lopinavir/ritonavir offered to Thailand and other middle-income countries. MOPH, Ministry of Public Health; CL, Compulsory licensing. Note: In May 2007, the Thai MOPH was still paying the price for LPV/r offered by Abbott in August 2006. Later offers by Abbott had conditions unacceptable to the Thai MOPH (no further price reduction and withdrawal of CL).

after pooled procurement negotiations, together with 65 other countries, facilitated by the Clinton Foundation (Fig. 1).

Discussion

Ensuring access to affordable generic medicines has been a cornerstone of Brazil and Thailand's universal access programmes. The long-term success of these programmes will be limited unless access to newer medicines is ensured.

Middle-income countries such as Brazil and Thailand are caught in a double bind. Because they have manufacturing capacity they are heavily pressured by pharmaceutical companies, backed by the US government, to increase intellectual property protection. At the same time, they are viewed as emerging economies with rich elites representing lucrative markets, and so are excluded from differential pricing policies offered to least-developed countries. The reality, however, is that HIV/AIDS is overwhelmingly a disease of the poor. Brazil and Thailand provide ART free to patients, but public health services in these countries are unable to pay the high prices demanded by multinational pharmaceutical companies. These concerns are not limited to antiretroviral medicines, but extend to all essential medicines.

The right of governments to override patents to protect public health is clearly established in international trade law, as affirmed by the 2001 Doha Declaration on TRIPS and Public Health, and has been promoted by

international institutions including the World Bank, WHO and the United Nations Development Programme. In practice, however, developing country governments have been pushed through trade pressure to implement much stricter intellectual property protection than required under international agreements. They are also subjected to further pressure not to use public health safeguards when patents become a barrier to accessing essential medicines. Abbott's actions against Thailand are the clearest demonstration of this disregard for the public health safeguards in the patent system.

Experience shows that negotiations with pharmaceutical companies alone have largely failed to secure optimal prices. By relying on this strategy, Brazil is currently paying up to four times more for second-line drugs compared with prices available internationally. Company deals have also stunted the development of local generic manufacturing capacity, and this is reflected by the fact that no new generic AIDS drug has been produced in Brazil since 2002. Thailand spent several years negotiating with companies who failed to offer reasonable prices, and this has limited treatment access for patients. By issuing compulsory licences, the Thai government has given a clear indication to generics manufacturers both in the country and abroad that generic production is worthwhile.

The importance of compulsory licensing to the sustainability of treatment programmes was highlighted by a recent World Bank evaluation of Thailand's national HIV/AIDS programme. It stated: 'Because Thailand stands to gain a great deal from bilateral agreements to reduce trade barriers with trading partners like the United States, the Royal Thai Government may be tempted to relinquish its rights to grant compulsory licences for AIDS drugs in exchange for proffered trade advantages. The report finds that the cost of such concessions would be large. For example, by exercising compulsory licensing to reduce the cost of second-line therapy by 90%, the government would reduce its future budgetary obligations by 3.2 billion discounted dollars through 2025.' [10].

Whereas many of the lessons presented in this article do not directly apply to all developing countries, the majority of whom do not currently have adequate pharmaceutical manufacturing capacity, it is clear that the compulsory licences issued by Thailand have had important international repercussions: the price offered to Thailand for efavirenz motivated the Brazilian government also to pursue compulsory licensing, and the compulsory licence for lopinavir/ritonavir forced Abbott to reduce its price in over 40 countries. Finally, by issuing compulsory licences the Thai and Brazilian government has sent a clear message to generics companies both in country and abroad that generic manufacture is worthwhile; this will increase the availability of generic medicines that can be imported by other countries through compulsory licensing.

Brazil and Thailand are not alone in facing these challenges. India is another country with strong domestic drug production capacity. The country has a weak national HIV/AIDS program compared to Brazil and Thailand [51], but is an important exporter of generic antiretroviral drugs, currently providing approximately half of all antiretroviral medicines used in the developing world. India only met TRIPS requirements in 2005, and it remains unclear which medicines will be granted patent protection, and to what extent public health safeguards will be effective. These are critical issues for HIV/AIDS treatment programmes across the developing world.

An informed and engaged civil society is essential to supporting governments in putting health before trade, and speaking out against pressure from industry and developed country governments. As the need for newer antiretroviral drugs increases, so the efforts of civil society will be more necessary than ever.

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