

Expanding Global Access to ARVs: The Challenges of Prices and Patents

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Michael R Reich

Harvard University Center for Population and Development Studies, Cambridge, Massachusetts, USA

Priya Bery

Director of Policy & Research, Global Business Coalition on HIV/AIDS, New York, USA

Michael R Reich, PhD is Director of the Harvard Center for Population and Development Studies and Taro Takemi Professor of International Health Policy at the Harvard School of Public Health. He recently edited a book on public-private partnerships for public health (distributed by Harvard University Press, 2003) and is co-author of *Getting Health Reform Right: A Guide to Improving Performance and Equity* (Oxford University Press, 2004). He received his PhD in political science from Yale University and has been a faculty member at Harvard University since 1983.

Priya Bery, SM is Director of Policy & Research at the Global Business Coalition on HIV/AIDS, a New York-based alliance of international companies fighting the pandemic. She works to advance partnerships between business and government in Asia and other regions heavily affected by HIV/AIDS. Ms. Bery received her Master's of Science in Health Policy and Management from Harvard University in 2001, where she focused her research on HIV/AIDS and access to medicines. Prior to her study in public health, she worked on health and environmental legislation in the U.S. Senate as well as in development on maternal and child health issues in India.

In the first years of the twenty-first century, access to AIDS medicines reached the top of the global health policy agenda. In developed countries, expanded access to new medicines occurred in the mid-1990s and contributed to dramatic reductions in deaths due to AIDS (Mocroft *et al.*, 1998). In the United States, for example, AIDS mortality rates decreased by 75 per cent between early 1994 and mid-1997 – a decline attributable in large part to the intensive use of antiretrovirals (ARVs) (Palella *et al.*, 1998). Since 1997, the US Food and Drug Administration approved over 50 therapies that can slow or disrupt viral replication or treat opportunistic infections. These AIDS drugs included three types of ARVs (nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors) used in various combinations. With these new medicines and falling prices, the treatment of people living with HIV/AIDS became increasingly cost-effective. AIDS interventions in developed countries, including the delivery of highly active antiretroviral therapy (HAART), produced dramatic survival benefits and averted many long-term costs related to opportunistic infections and hospitalization.

While AIDS medicines became available to most people living with HIV in the developed world (Rose, 1998; UNAIDS, 2000b, p. 86), they have remained difficult to obtain in most developing countries. Nevertheless, in the past decade a sea change occurred in global policy and thinking about access to AIDS medicines for the world's poorest countries. Previously, many people wondered if it was feasible or desirable to treat AIDS patients in poor countries. Today, many people expect and demand expanded access to AIDS medicines for patients throughout the developing world. This chapter provides an historical perspective on how progress was achieved in addressing the challenges posed by two key dimensions affecting access to ARVs in developing countries: prices and patents. The chapter also demonstrates how major obstacles were recognized and confronted through a contentious and iterative political process.

Expanding Access to Treatment

Of the world's estimated 34–46 million people living with HIV in 2003, over 95 per cent live in the developing world, with 25–28 million in sub-Saharan Africa (UNAIDS/WHO, 2003). Adult infection rates in sub-Saharan Africa are strikingly high – for example, 38.8 per cent of adults in Botswana are living with HIV/AIDS and 20 per cent of adults in South Africa – compared with 0.6 per cent in the US and 0.1 per cent in the UK (UNAIDS, 2000c). Of the total infected population globally, it is estimated that approximately 6 million people are in need of treatment in low and middle-income countries, since ARV therapy is initiated after a certain stage in disease progression. Yet only 400 000 individuals had access in late 2003 (WHO, 2003). The need is greatest in Africa, where the epidemic has

advanced relentlessly. At the end of 2003, only 100 000 people had access to ARVs in sub-Saharan Africa (about 2 per cent of the 4.4 million people estimated in need), although this represented a substantial increase from only 30 000 people with access to treatment in 2001 (UNAIDS/WHO, 2003).

Why are these life-saving drugs not reaching those who need them? As explained throughout this book, various factors have combined to limit access to AIDS medicines in poor countries. The main obstacles include overwhelming national poverty, the epidemiology of the disease, the economics of the medicines, and the problems of health care systems in developing countries. Other factors have also shaped the limited access, including economic stagnation, political instability, and the devastating impact of stigma and discrimination, discouraging individuals from getting tested and seeking care, support, and treatment. The reluctance of political leaders and governments to respond publicly and aggressively to the HIV/AIDS pandemic has delayed the effective implementation of national policies (Caldwell, 2000). Even when some leaders have decided to fight the epidemic, the commitment of resources has often lagged behind. Tragically, the countries most affected by the AIDS epidemic have confronted the greatest problems in providing access to AIDS medicines.

In the past few years we have seen increasing leadership by governments, international institutions, private companies, and civil society to expand access to ARVs in the countries that need the medicines most. In September 2003, the World Health Organization announced a global program of '3 by 5' to provide 3 million people with ARV treatment by 2005. The United Nations' Millennium Development Goals give high priority to efforts that can halt and reverse the spread of HIV/AIDS by 2015. New partnerships, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, have emerged to help achieve these goals. And individual donor countries have made new financial aid commitments, such as the US\$15 billion in the US President's Emergency Plan for AIDS Relief, known as PEPFAR, which announced its first grants in February 2004. Corporations have also made new investments to extend treatment to employees, families, and local communities. These efforts are designed to scale up access to ARVs, which otherwise, according to WHO estimates, could only reach less than one million people in the developing world by the end of 2005.

Affordability of medicines has been at the center of the debate over access to AIDS drugs in poor countries. This chapter explores the high cost of drugs to show how the debate evolved and how key issues have been addressed. We discuss how drug prices are set, and how patents affect the price of pharmaceuticals. We review five policy options for price and patent issues in expanding access to AIDS medicines in developing countries. We conclude with an assessment of other obstacles to access, in the context of the sharply reduced prices of AIDS medicines over the past decade. These other issues must be resolved to achieve sustained access to AIDS medicines in resource-limited environments.

Pricing Pharmaceuticals

In developing countries, most medicines are purchased by households with personal funds or less frequently by governments with public budgets (WHO, 1998). Both personal funds and government budgets are severely limited. For example, during the 1990s, average total health expenditure (public and private) per year was US\$14 per person in Uganda and US\$246 per person in South Africa, compared with US\$4080 in the United States (World Bank, 2000). In sub-Saharan Africa, nearly 46 per cent of people live on less than US\$1 a day (UNDP, 2001, p. 10). Poverty thus makes it impossible for individuals or governments to pay for the medicines that are needed.

For AIDS, the standard treatment in developed countries in the mid-1990s was HAART, which at that time cost up to US\$21 000 per person per year (Freedberg *et al.*, 2001). Who paid for treatment critically affected access. In developed countries, most HIV patients received AIDS care and treatment through government programs or private insurance. In most developing countries, by contrast, only a small number of HIV patients received treatment through personal funds or through very limited programs run by governments or companies, while the vast majority of patients received no effective treatment at all. As a result, in the late 1990s, the call for expanded access to AIDS medicines in developing countries became a conflict over drug pricing.

In almost all countries around the world, there is public concern about the high price of pharmaceuticals because of financial strain on government health budgets and on household budgets for low-income patients. Most countries (other than the United States) regulate drug prices by implementing price controls, placing limits on company profits, or setting reimbursement rates under social insurance programs (Danzon, 2000). Governments struggle with a basic policy conflict between reducing drug prices to contain health expenditures and expand health services, and raising drug prices to create incentives for new drugs or provide subsidies for local manufacturers.

In general, producers set prices for drugs to capture some combination of the costs of research, development, production and marketing – plus profits – and compete with other companies that manufacture the same or similar products. The total cost of developing a new drug is hotly debated. According to the Pharmaceutical Research Manufacturers Association, member companies invested US\$32 billion in research and development in 2002 (PhRMA, 2003). Joseph A DiMasi and colleagues estimate the full cost of developing a new drug at US\$802 million (including the costs of unsuccessful projects and opportunity costs) (DiMasi *et al.*, 2003). One co-author, Henry Grabowski, explained in another article that ‘new product approval incurred out-of-pocket costs of over \$400 million. This includes money spent in the discovery, pre-clinical and clinical phases as well as an allocation for the cost of failures’ (Grabowski, 2002, pp. 851–2).

Critics have countered that this figure overstates the costs of drug discovery and development (Young and Surrusco, 2001).

Prices for new drugs, however, do not always reflect full costs, as shown by the wide differences in prices for the same product. Prices for the same drug (produced by the same company) vary greatly both between and within countries, because of different corporate strategies, policy circumstances, tariffs, exchange rates, and negotiating conditions. For example, the list price of zidovudine (AZT), an ARV used in HIV combination therapy, was US\$1.71 per 100 mg capsule in the UK and US\$0.66 in Spain (in 2000) (UNICEF-UNAIDS *et al.*, 2001). According to Danzon and Kim (1998), comprehensive price comparisons of international drug prices incorporate a host of methodological issues involving measurement differences in average price levels. These problems can produce different results (depending on how they are addressed) and can undermine the validity of policy conclusions from price comparisons.

Multinational companies that develop new drugs seek to set high prices for their products in major markets (such as the United States) as a way to achieve high returns on the costs of drug development and marketing (Danzon, 2000). Markets with high prices thus pay a higher share of corporate research and development costs, leading to US charges of free-riding by European (and other) governments and consumers (Editorial, 2002). This situation has created an 'imbalance' in pharmaceutical innovation between the United States and Europe, with a recent report identifying possible negative consequences for Europeans due to delayed access to drugs, poorer health outcomes, and lower investments in research (Gilbert and Rosenberg, 2004).

Governments in poor countries typically have limited leverage in negotiations with pharmaceutical companies over prices, especially for single-source products (produced by a single company under a product patent). All developing nations account for only 16 per cent of sales in the global pharmaceutical market, with Africa representing only 1.3 per cent (IMS Health, 2002). Consequently, prices in poor countries often end up close to those in rich countries, and they can even exceed prices in rich countries when customs, tariffs, distribution, and pharmacy charges are included. For many poor countries, difficulties in negotiating lower prices for AIDS medicines (and other drugs) are also related to the nation's overall poverty, generally small market size, inefficient pharmaceutical purchasing system, and limited domestic pharmaceutical production capacity.

Responding to International Pressures to Lower Prices for AIDS Drugs

The past decade has witnessed a surge of international pressure to lower the prices for AIDS medicines in developing countries (Figure 13.1). Pressure came

from AIDS activists, people living with HIV/AIDS, generic pharmaceutical companies, and non-governmental organizations (including Médecins Sans Frontières, Consumer Project on Technology, ACT-UP, and the Treatment Action Campaign). Activists and world leaders including Nelson Mandela drew global media attention to this issue in their opposition to the lawsuit brought (and eventually withdrawn) by 39 drug manufacturers against the South African government's Medicines and Related Substances Act of 1997, which sought to expand access to low-cost AIDS medicines through various measures (Park, 2002; Sidley, 2001). The activist pressure helped place the issue of access to AIDS medicines high on the international health agenda and onto the policy agenda of the United Nations and the G-7 countries in the last years of the twentieth century.

Facing these pressures, international agencies and pharmaceutical companies responded by setting up new mechanisms that promised to expand access in developing countries and by reducing some prices. The first effort to expand access was a UNAIDS project in Uganda and Côte d'Ivoire in 1997, called the Drug Access Initiative. In Uganda, for example, prices for a first-line regimen declined from about US\$12 000 per year in 1997 to about US\$7200 per year in 1999 (Okero *et al.*, 2003, p. 7). A more formalized process was established in May 2000 through the Accelerating Access Initiative (AAI). Through AAI, UNAIDS along with other co-sponsoring international agencies and six pharmaceutical companies set up a preferential pricing mechanism at the country level. As of June 2002, 19 countries had signed agreements on significantly reduced drug prices (WHO, 2002). These two efforts helped expand the delivery of AIDS medicines to HIV patients in participating countries, reaching about 76 000 people in Africa by June 2003 (IFPMA, 2003), still a small proportion of the people needing treatment. The two initiatives also marked major shifts in the global

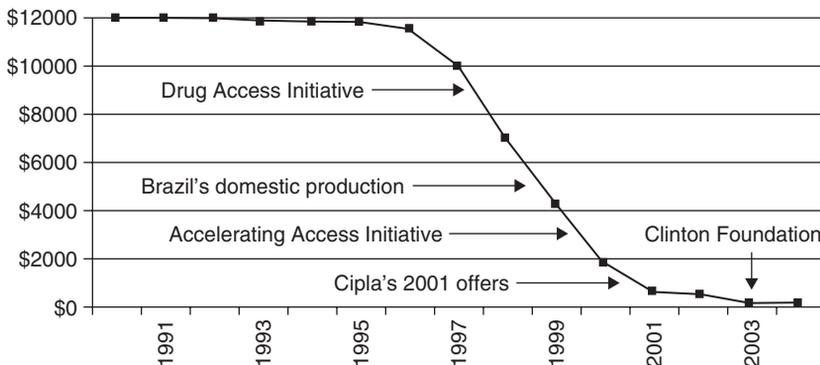


Fig. 13.1 Annual cost per person for triple-drug therapy in Africa (US\$). Adapted from Quick (2001).

debate, making it legitimate to question the high prices of AIDS drugs for poor countries.

The first developing country to make a full-scale national commitment to provide universal and free access to ARVs for AIDS patients was Brazil. Brazil's 1988 constitution guarantees universal access to health care, and in 1996 Brazil passed a law that assures universal access to antiretrovirals (Lei no 9.313.996). This high-level political commitment was critically important for Brazil's efforts to expand access to treatment for people living with HIV/AIDS. The Brazilian government's policy of developing capacity for local production of generic products and its threats of compulsory licensing helped push down domestic prices for AIDS medicines (and raw materials) (Teixeira *et al.*, 2003). These strategies reduced the cost of ARVs in Brazil, although questions remain about how the country will sustain its national treatment program over the long term. Between 1996 and 2001, the average cost of treatment per patient decreased by more than 50 per cent in Brazil (Teixeira *et al.*, 2003, p. 82). Four years after the national treatment program was introduced, AIDS-related mortality had fallen by about 50 per cent, and each AIDS patient was only a quarter as likely to be hospitalized compared with the time before the national treatment program began (Rosenberg, 2001).

Brazil has been widely cited as a model of policy response for developing countries. But Brazil's response is not easily replicable in Africa, because of important differences: Brazil's relatively low prevalence of HIV (0.7 per cent in 2002 (UNAIDS, 2000c)), the country's relatively high income (US\$2830 per capita in 2003), the strong national pharmaceutical industry, and its use of three World Bank loans to help finance the AIDS control program: US\$160 million in 1993, followed by US\$165 million in 1998, and an additional US\$100 million in 2003 (World Bank, 2003)). Brazil also has a strong civil society movement that effectively put pressure on the government to adopt universal access to ARVs as official policy. Despite these differences, the Brazilian government is helping African countries expand their access to AIDS medicines, for example, by working with the government of Mozambique to develop generic production capabilities and in the interim provide them with Brazilian manufactured generic medicines (Associated Press, 2003).

India has also played an important role in reducing prices for AIDS medicines. Drug producers in India began to manufacture ARVs in the late 1990s, initially focusing on the domestic market and then exploring export opportunities. These generic AIDS drugs were not covered by product patents in India. In February 2001, Cipla, an Indian generic manufacturer, offered to sell ARV combination therapy at US\$350 per person per year to Médecins Sans Frontières (MSF) and at US\$600 per person per year directly to governments in poor countries (McNeil, 2001; UNDP, 2001, p. 106). At the time of the Cipla announcement, the lowest market price worldwide for triple combination therapy was just under US\$10 500. Within one year, the lowest price for triple therapy had dropped to US\$727 per

person per year, a result of international pressure and competition by low-cost generics (Médecins Sans Frontières, 2003). WHO supported the role of generic manufacturers by including them in companies reviewed in the first international quality assessment of AIDS medicines in May 2001. In 2003, an updated version of this list included 74 products from 11 manufacturers (both branded and generic) for 11 ARVs and four combinations (WHO, 2003).

After the United Nations Special Session on HIV/AIDS in June 2001, a number of new partnerships and multisectoral coalitions emerged to help expand global access to ARVs, addressing both the cost of medicines and problems in delivery. The Global Fund to Fight AIDS, Tuberculosis and Malaria was established in January 2003 and allocated about US\$2.1 billion in its first three rounds of grants, with about 59 per cent directed toward HIV/AIDS. The Global Fund estimates that an additional 500 000 people will receive ARVs over the next five years through Fund-supported programs. In May 2003, US President George Bush signed into law a five-year, US\$15 billion commitment to fight HIV/AIDS in Africa and the Caribbean, which seeks to provide treatment to 2 million people. The business community is also working to increase the reach of treatment programs in partnership with the public sector, through such groups as the Global Business Coalition on HIV/AIDS (2003). For example, the mining company Anglo American is extending its employee treatment programs to the surrounding communities in South Africa through a new co-investment scheme with the Global Fund, the Henry J. Kaiser Foundation and the Nelson Mandela Foundation.

In the fall of 2003, prices for AIDS medicines dropped again, when the William J. Clinton Foundation announced a new partnership with Indian and South African generic producers and community organizations to provide triple-drug therapy at 38 cents per patient per day in Africa and the Caribbean. At these prices, the generic drug costs of AIDS treatment were cut by nearly 60 per cent (from the prevailing price of about US\$1 a day). Until the Clinton effort, the lowest available price of the same three-drug regimen using brand-name ARVs was US\$1.54 per patient per day (Schoofs, 2003). The new prices brokered by the Clinton Foundation will challenge the generic industry to deliver a continuous supply of high-quality drugs. But if sustainable, the prices could catalyze expanded access to treatment in a number of poor countries.

In May of 2004 the US government announced a major shift in AIDS policy to encourage the development of fixed dose combinations (FDCs) of ARVs. The government created a Fast Track Review System for AIDS Drugs designed to reduce approval time to six weeks. FDCs are single pills containing two or three drugs included in ARV triple combination therapy. At the same time, Bristol Myer-Squibb, Gilead, and Merck & Co., three manufacturers of branded ARVs, announced that they would work together to develop a combined, once-daily tablet. This is the first collaboration between patent-holders making single components of ARV triple therapy. People living with HIV/AIDS will benefit from simplified treatment regimens and potential cost savings by purchasing one pill

instead of each drug separately. Fixed dose products have already been developed by Indian generic manufacturers and have been prequalified for first-line treatment in resource-limited settings by the WHO. Although these FDC products are currently used by people in developing countries, they are not permitted in the US President's Emergency Plan for AIDS Relief until they have been approved by the US government's new fast track program.

This review shows how prices for triple-drug AIDS therapy dropped dramatically in just four years, from 1999 to 2003, as prices fell up to 98 per cent – from US\$12 000 a year to less than US\$200 a year. Prices for a number of ARVs in many developing countries are now probably close to the marginal costs of production. These remarkable price declines have reduced price as a barrier to access for AIDS medicines for governments and many patients in developing countries. However, even at these lower prices, the cost of AIDS medicines remains far beyond the ability to pay for most people in developing countries except for the elite. Other obstacles also remain, including the lack of funding for AIDS medicines, debate among donors on the use of generic medicines and the lack of adequate facilities to treat and care for patients (as we discuss below). Moreover, pricing will persist as an important question for the next generation of ARVs, which are not covered by current agreements and policies. Prices for triple-drug therapy will also vary depending on the drug combination selected. Finally, if drug resistance increases, there would be a growing need for second-line (new) ARVs. A recent study in Europe reported a 10 per cent rate of HIV drug resistance for first-line drugs in newly infected individuals (van der Vijver *et al.*, 2003).

A critical factor that affects the pricing of new drugs is how the patent system operates at the national and international levels; we turn to this issue next.

How Patents Affect Drug Prices

The international patent system has been a major focus in the debate over access to AIDS medicines in developing countries. The past three decades have shown a global trend toward increased patent protection of pharmaceuticals, with a new international regime emerging since 1995, seeking to include more developing countries. This trend has been promoted by the international pharmaceutical industry, while critics (especially in the past decade) have argued that expanding patent protection has limited access to AIDS medicines by limiting competition from non-patented copies and thereby supporting high prices.

A patent is a set of legal rights, based on national law, providing the patent owner with the means to prevent others from making, using or selling a new invention for a limited period of time (for example, 20 years) (WTO, 2001b). These national laws operate within the rules of the international trade regime, which seeks to establish some consistency across national boundaries. Patents are intended to

provide a balance between protecting economic incentives for innovators and promoting the public interests of society. Patents represent a form of intellectual property rights (IPR), which are designed to assure inventors that they (and not others) will receive economic returns on their innovative ideas, as a way of creating incentives to develop new products. (Other forms of intellectual property rights, such as trademarks and copyrights, are not considered in this chapter.) At the same time, the patent system allows public access to knowledge about innovations, as a way of promoting continued research and development by other parties.

National patent laws differ country by country. In general, rich countries tend to provide stricter protection of intellectual property rights, while poor countries tend to have limited protection and less effective mechanisms for enforcement. Not surprisingly, rich countries also tend to produce more intellectual property, and therefore have groups and individuals with strong incentives to seek effective protection. Countries at different levels of technological development thus have different needs and desires about a national patent system (Commission on Intellectual Property Rights, 2002).

For medicines, patents can be applied to new products, as a *product patent* for the chemical entity in a new drug, or to new processes, as a *process patent* for the method of producing the chemical ingredients for a medicine (WTO, 2001b). In general, poor countries seek to weaken the patent system, to promote cheap imports or allow the production and sale of cheap copies. They may then introduce a process patent system, as domestic companies are able to produce copies of existing products (which often are protected by product patents in other countries). Once a country's pharmaceutical industry can invent new products, the country typically changes its laws and moves to a product patent regime. Japan, for example, introduced product patents in 1976 (Reich, 1990), followed by Switzerland in 1977, Italy, Holland, and Sweden in 1978, and Canada and Denmark in 1983, with China in 1992–93, Brazil in 1996, and Argentina in 2000 (Lanjouw, 2003) (see Table 13.1).

Advocates for expanded access have argued that the international patent system, by supporting high prices and blocking the production and importation of generic medicines, has obstructed developing countries from obtaining cheaper AIDS medicines. According to these advocates, the obstructive role of patents has been enhanced by recent changes to strengthen the international patent system, which have been supported by the multinational pharmaceutical industry and by rich country governments (especially the United States). In short, advocates have argued that the patent system has protected the profits of drug companies in rich countries while ignoring the lives (and deaths) of HIV patients in poor countries.

Advocates for strengthening the international protection of patents, on the other hand, have argued that these intellectual property rights are essential as incentives to develop new medicines (including AIDS medicines). The research-based pharmaceutical industry has lobbied fiercely and effectively to enhance patent protection in international agreements and national laws around the world.

Table 13.1 Introduction of production patent protection and GDP per capita.

Country	Year of adoption	GDP per capita (1995 US\$)
OECD countries		
Japan	1976	24 043
Switzerland	1977	36 965
Italy	1978	13 465
Holland	1978	20 881
Sweden	1978	21 896
Canada	1983	16 296
Denmark	1983	28 010
Austria	1987	25 099
Spain	1992	14 430
Portugal	1992	10 469
Greece	1992	10 897
Norway	1992	30 389
Recent Adopters		
China	1992–3	424
Brazil	1996	4482
Argentina	2000	8100
Uruguay	2001	6208
Guatemala	Future	1545
Egypt	Future	1191
Pakistan	Future	508
India	Future	450
Malawi	Future	156

Note: China GDP is for 1992; for countries adopting after 1992, the GDP per capita figure is for 1999. From Lanjouw (2003).

In short, the research-based pharmaceutical industry views the patent system as the essential cornerstone for their continuing drug development and commercial success (IFPMA, 2004). They argue more broadly that patent protection helps to promote economic development by providing incentives for innovation and investment (Rapp and Rozek, 1990). In brief, they argue that without product patents there would be few new drugs.

International Agreements Affecting Patents: The WTO and TRIPS

New institutions and mechanisms have been developed to address the differences in patent protection among nations and resolve conflicts that occur. The most

important institution is the World Trade Organization (WTO), which was established as the global governing body of the international trade regime in 1994 as a result of the Uruguay Round of the trade negotiations in the General Agreement on Tariffs and Trade (GATT). The WTO sets the legal ground rules for international trade and promotes the objectives of non-discrimination, liberalization of trade barriers, competition, and transparency. As of April 2003, the WTO had 146 member countries.

Intellectual property standards for WTO members are established through the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) of 1995. This mechanism sets a floor of IPR protection for countries and connects IPR to several international trade agreements. Prior to the TRIPS Agreement, over 40 countries (primarily poorer countries) did not provide any comprehensive product and process patent protection for pharmaceuticals (WHO, 2001). Under TRIPS, member nations are required to adhere to basic minimum standards for universal patent protection for any technological invention, including pharmaceuticals. Failure to comply with these rules brings the threat of trade sanctions and other adverse consequences. The expansion of patent protection through TRIPS drew broad support from the research-based pharmaceutical industry, which expected to benefit from increased protection of its patents around the world.

Countries that previously had no patent protection are now introducing it so that they can become members of the WTO. TRIPS provides some leeway for countries to bring their national legislation in compliance with agreement standards. The length of the period varies for developed and developing countries. Developed nations were required to apply all TRIPS provisions by 1 January 1996, one year after TRIPS was established; developing countries and transitional economies were given five years, until 1 January 2000; and least developed countries were given 11 years, until 1 January 2006 (WHO, 2001).

The 4th WTO Ministerial Conference, held in Doha, Qatar, in November 2001, extended this deadline until 2016 for the world's least developed countries. The meeting also produced the Doha Declaration on the TRIPS Agreement and Public Health, which asserted a priority to public health over intellectual property (WTO, 2001a). The Declaration stated, 'The TRIPS agreement does not and should not prevent Members from taking measures to protect public health', adding that TRIPS should be implemented in a manner 'supportive of WTO Members' right to protect public health and, in particular, to promote access to medicines for all'. The interpretation of the Doha Declaration in practical policy subsequently became a matter of vigorous debate. The Doha Declaration did not establish any new principles for TRIPS. Rather, it re-stated ideas contained in TRIPS and recognized that the poorest countries (without a well developed domestic pharmaceutical industry) 'could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement' to gain access to medicines. In short, could a poor country use compulsory licensing under a public health emergency to import generic drugs that were protected by product

patents (in the importing country), and if so, for which diseases and from which countries?

In August 2003, the WTO resolved some of these questions raised by the Doha Declaration. Without changing the TRIPS Agreement, the WTO General Council approved a statement supporting the importation of generic medicines into those developing countries that lacked pharmaceutical manufacturing capabilities, under certain conditions (WTO, 2003b). This represented an interim decision, intended to last until TRIPS is amended in the ongoing round of negotiations. The WTO declared that the decision removed the final 'patent obstacle' to cheap drug imports for poor countries. The WTO Director-General announced:

The final piece of the jigsaw has fallen into place, allowing poorer countries to make full use of the flexibilities in the WTO's intellectual property rules in order to deal with the diseases that ravage their people.... It proves once and for all that the organization can handle humanitarian as well as trade concerns (WTO, 2003a).

How TRIPS Affects Access to ARVs

The debate over intellectual property rights and ARVs produced intense advocates on both sides. Supporters of IPR argued that strict enforcement of IPR is necessary for innovation and continued economic and social development, while critics of IPR countered that patent protection interferes with progress in human development in poor countries (UNDP, 2001, p. 103) by obstructing access to needed medicines and other products.

The TRIPS Agreement of 1995 is often interpreted as allowing for two mechanisms that could be used to expand access to cheaper versions of patented drugs:

- A *compulsory license* allows a government to grant a license to use a patent without permission of the patent holder, when the patent holder is either not using the patent within the country or not using it adequately (according to Article 31 of the TRIPS Agreement on 'other use without authorization of the right holder'). Under TRIPS, a compulsory license can be granted under certain circumstances, such as a national emergency or other circumstances of extreme urgency, and in the case of anti-competitive practice by the patent holder. This license would require that compensation be paid to the patent holder. The United States has used compulsory licenses for various technologies in the computer, recording, defense and other industries.
- *Parallel importation* provides access to lower-priced patented drugs by purchasing products marketed by the patent owner in one country (where they are sold at a lower price, such as Spain) and importing them into another country (where they are sold at a higher price, such as Britain) without the patent

owner's approval. Article 6 of TRIPS, by not settling or expressly prohibiting parallel imports, is interpreted as allowing for this kind of arbitrage.

The first case of a government's seeking to use compulsory licensing for ARVs occurred in August 2001, when Brazil's Ministry of Health announced steps to produce nelfinavir, a drug patented by Roche Laboratories, in a Brazilian government production facility in order to reduce the drug's price (Rich and Petersen, 2001). In 2000, Brazil had spent US\$303 million on AIDS drugs, with about US\$88 million (or 25 per cent of the total) on nelfinavir (Rich and Petersen, 2001). Roche responded to the government's announcement about compulsory licensing by offering to reduce the product's price in Brazil (more than the 13 per cent it previously offered, which the government had rejected as inadequate) – and an agreement was reached without a change in government policy. This case shows that countries like Brazil (with substantial resources, a domestic industry, political mobilization, and a large market) can use threats of compulsory licensing as leverage in price negotiations to achieve greater discounts. However, only a few developing countries resemble Brazil in these respects.

In March 2004, the government of Mozambique issued a compulsory license for manufacturing a triple combination of antiretroviral drugs to meet national needs. In doing so, Mozambique became the first African country to take this important step in implementing the Doha Declaration. Prior to this, no developing country had successfully used compulsory licensing or parallel importation to expand access to ARVs. However, the efforts by Brazil (and South Africa, as noted below) to implement national policies based on these two mechanisms advanced the international debate on access, even though the policies were not adopted. Later in 2004, several other developing countries issued a compulsory license for an AIDS medicine – and more are expected, especially if this mechanism proves to be effective in expanding access in practice.

Patents for AIDS Medicines

To what extent has the protection of patents affected access to ARVs in developing countries, especially since the start of TRIPS in 1995? A first step in answering this question is identifying where pharmaceutical companies have filed for patent protection for their products in developing countries. An analysis of 15 ARVs in 53 African countries found that eight products were patented in three or fewer countries, and four products were patented in 24–33 countries (Attaran and Gillespie-White, 2001). The authors suggested that these findings indicated a limited impact of patents on access. The study also found, however, that over half of the 53 African countries had patents on zidovudine and nevirapine, the two most commonly used drugs in combination treatments in developing countries,

suggesting an important impact of patents for certain products in some countries (Boelaert *et al.*, 2002).

This study, designed to assess the impact of patents on the availability of AIDS drugs in Africa, generated significant controversy. On the one hand, the study supported the idea that pharmaceutical companies typically file for patents in countries where they expect significant sales. But the results also showed that some companies filed for patent protection in African countries where significant economic returns were unlikely (UNDP, 2001, p. 107). For example, one company (GlaxoSmithKline) filed for patents for two products in 33 and 37 African countries, including many that are unlikely to show significant sales volumes (such as Burundi, Comoros, Madagascar, and Rwanda). This finding suggests that other factors (in addition to expected markets and sales) can affect a company's decision to file for product patents in specific countries.

More generally, the impact of patents relates to the demand for medicines. In the developed world, strict patent protection does not affect demand or consumption because most consumers do not face the full cost of the drug (due to insurance coverage). In developing countries, most consumers must pay the cost of treatment out of pocket and therefore are not insulated from the costs of medicines. Inadequate health systems, lack of insurance and low wage rates exacerbate the impact of patents (through high prices) on access to treatment.

In developing countries where a significant national pharmaceutical industry exists (such as South Africa and Brazil, where local companies can produce some active ingredients) and a national patent system exists, patents can pose (and arguably did pose) an obstacle to access for ARVs through high prices. In those countries, the patent system prevents the production of patented ARVs as generic drugs. In such situations, countries have three options that comply with international trade law. First, they can manufacture AIDS drugs that were introduced *before* the start of product patent protection – as Brazil did for products before 1995 (when Brazil implemented product patents). Second, they can pressure companies to reduce their prices – again, as Brazil did through threats of compulsory licensing. Or third, countries can pass national legislation or declare a public health emergency in order to produce (or import) the drugs under a compulsory licensing system.

The application of trade strategies (like compulsory licensing and parallel imports) to expand access to ARVs generated a number of international conflicts. Developed countries (especially the United States) have threatened to cut foreign direct investment or retaliate in other ways if developing countries neglect or dilute patent protection (UNDP, 2001, p. 107). For example, the United States placed India, Thailand, and South Africa on the US Trade Representative's Special 301 Watch List in May 1998, because of the lack of adequate intellectual property protection. For South Africa, the United States objected to a 1997 amendment to the Medicines and Related Substances Act that appeared to allow the South African Minister of Health to revoke patent rights, in allowing for parallel

imports, compulsory licensing, and registration of generic drugs (United States Trade Representative, 2000, p. 371).

Approaches for Expanding Access to Medicines for HIV/AIDS

Five broad approaches can be considered for expanding access to ARVs in developing countries: market-based approaches, differential pricing, trade policy-based approaches, bulk purchasing, and donations. The sustainability of each strategy depends not only on the affordability of the medicines but also on the ability to maintain incentives for future research and development by the pharmaceutical industry. Some of these approaches are being implemented, while others represent proposals that could be adopted. We briefly review each approach's advantages and disadvantages.

Market-based Approach

In a market-based approach, prices are set by companies, either through independent company decisions (as occurs mostly in the United States) or through negotiated agreements for each drug with governments and insurance providers. Governments can then purchase ARVs and other AIDS drugs according to their national priorities for AIDS and their health budgets. Brazil, for example, followed a market-based approach (by purchasing some products on international markets) but combined this with a trade policy-based approach (of threats to use compulsory licensing) along with external financing from World Bank loans and local production of certain AIDS medicines. A variation on a market-based approach is to support the creation of a global market for raw materials, which are then formulated into final products by local manufacturers. The WTO's 2003 interpretation of the Doha Declaration in effect allows the development of an international market of generics for the world's poorest countries through compulsory licensing mechanisms.

The primary disadvantage of this approach is that global inequities in drug access could continue for poor countries due to their limited capacity to negotiate with international companies and their limited budgets for AIDS care and treatment. The situation could change if companies continued to offer steep discounts in drug prices (for future as well as current products), if compulsory licensing through imports becomes feasible administratively, and if the Global Fund and donor governments offer adequate financing for AIDS-affected countries to procure ARVs. Though progress has been made, and the current price discounts have produced an expansion in access to AIDS medicines in developing countries, huge gaps remain.

Differential Pricing

Differential pricing is a pricing system in which a significantly lower manufacturer's selling price is established according to a country's socioeconomic status (WHO and WTO, 2001). More generally, companies often charge different prices in different markets based on how much the market will bear. This method could also serve as a strategy for companies to maximize profits by increasing sales in each market and in previously inaccessible markets (Sherer and Watal, 2001). This method can also be used to set prices based on ability to pay in resource-poor settings, in order to expand access – and in those instances, it is sometimes called 'equitable pricing' (Grace, 2003).

For this pricing system to be sustainable, however, shipments between national markets would need to be prevented, so that products offered at lower prices in poor countries would not be resold in rich countries. This system can require a high level of cooperation among governments and patent holders, to assure that appropriate regulations and safeguards are effectively implemented. In countries with well-established drug regulatory systems, such as the OECD countries, this movement of products can be effectively controlled.

Price differentials can also have important political ramifications, as shown by US senior citizens who travel to Canada and Mexico to purchase cheaper drugs, and by the current policy debate over prescription drug prices in the United States (Ulik, 2003).

Differential pricing is often opposed by producers, but it can bring them some benefits by providing entry to new markets, expanding the volume of sales, and producing higher profits if priced above marginal cost. An important question is how prices would be set in a differential pricing system. Three options are:

1. *Internal company policy*: In this method, each company decides on its own criteria for price differentials. For example, Merck established a company policy to discount their ARV prices based on the UNDP's Human Development Index (HDI) and the level of AIDS incidence in each country (J Sturchio, personal communication, 2001). (The UNDP's HDI is a composite single-number ranking of countries based on life expectancy at birth, level of education and income per capita.)
2. *International-agency-facilitated price negotiations*: In this method, an international agency facilitates price negotiations for each country and each company. For example, UN agencies are working with six pharmaceutical companies on the Accelerating Access Initiative to secure reduced drug prices at the country level (UNAIDS, 2001). (Implementation of these agreements, however, has been slow and so far only a limited number of patients have received treatment.) Within such programs, companies have avoided joint discussions and decisions on price differentials, because such discussions can be illegal under anti-trust law (UNAIDS, 2000a).

3. *Distribution of price information*: Distributing information about prices of high-quality AIDS medicines available in the international market can help correct information asymmetries and assist buyers in their procurement negotiations. For example, the WHO, UNICEF, UNAIDS, and MSF have produced a price list to provide market information about drugs used in the treatment and care of HIV/AIDS (WHO *et al.*, 2003).

Increasingly, civil society groups, international non-governmental organizations (NGOs), and the business sector are engaging in independent negotiations with pharmaceutical companies as shown by the efforts of MSF, the Clinton Foundation, and Anglo American, among others. This experience can also help inform various parties (including governments, Global Fund country coordinating mechanisms, NGOs, and private companies) about the range of pricing options for specific AIDS medicines.

Trade Policy-based Approaches

A third strategy is to use international trade agreements plus national pharmaceutical policies to expand access to AIDS medicines – through the promotion of voluntary license agreements, the purchase of generic drugs, and the development of differential patent systems.

1. *Voluntary license agreements*: This method permits individual companies or patent holders to license their patented technologies (both products and processes) to firms in developing countries (Friedman *et al.*, 2003). These license agreements can allow local firms to produce the same drug at lower cost and thereby sell the product at a lower price. This option allows the patent holder to maintain property rights in certain markets and may require payment of royalties to the patent holder. GlaxoSmithKline, for example, decided to issue a voluntary license for Combivir to a South African generics manufacturer and then waived its rights to royalties (Reuters, 2001). In exchange, the South African company agreed to pay 30 per cent of net sales to a local NGO working on HIV/AIDS.
2. *Compulsory licensing*: Under the TRIPS Agreement, a country can administratively decide to use compulsory licensing and allow the importation or local production of drugs in a public health emergency, in order to obtain lower prices without permission of the patent holder. Such agreements, while legal, can result in legal disputes between the patent holder and user and can cause conflicts between the developing country government and patent holders or their governments. Under TRIPS, compensation must be paid to the patent holder, although the amount is set by the national courts. As noted above, several developing countries have recently issued a compulsory license for AIDS medicines, and other countries have threatened to do so.

3. *Differential patent system*: In this proposal, patent holders would be encouraged to patent drugs only in countries where they believed there was a substantial market. This approach could emerge through voluntary decisions by patent holders or regulated through international agreements and governing bodies. One proposal encourages patent holders to protect property rights in rich countries or in poor countries, but not both (Lanjouw, 2001). This would provide companies with patent protection in developed country markets (where they have the vast majority of sales and profits) and would cede developing country markets (where they have limited sales and profits) to low-cost producers.

Bulk Purchasing

Bulk purchasing allows for collaborative pharmaceutical procurement among countries with similar needs. Purchases are pooled at a national level, thereby expanding demand for the product and increasing the negotiating capacity of purchasers. This approach carries the potential for drug expenditure savings and improved procurement practices and could be applied on a regional or a global level. Pooled purchasing could simplify procurement for pharmaceutical manufacturers, but holds the risk of creating distortions due to monopsony (when there is only one buyer in a market). This mechanism also brings the added difficulty of coordinating an already complicated procurement process across countries. Pharmaceutical companies do not generally consider this approach an attractive option.

One example of global bulk purchasing is the Global Drug Facility for TB drugs, which was established in March 2001. This organization has achieved a reduction in drug prices of 30 per cent, pushing the cost of a six-month course of treatment to about US\$10. The strategies have included a standardized set of drug products, a bulk-buying procurement system, and competitive bidding processes. In the first two rounds of applications, 12 countries were approved for support from the Global Drug Facility (Global Drug Facility, 2001).

A similar approach has been proposed for AIDS medicines through the Global Fund to Fight AIDS, Tuberculosis and Malaria. For example, a central procurement and distribution agency could help secure low prices for AIDS medicines through bulk purchasing agreements and could assure that recipients adopt integrated treatment and prevention regimens. Due to the challenges of bulk purchasing, the Global Fund currently supports procurement at the national level through bilateral agreements between governments and manufacturers.

Donations

Donations provide access to medicines through contributions from governments, NGOs, foundations, and corporations. A number of public-private partnerships

have been established to expand access to AIDS medicines (IFPMA, 2001). These programs include Boehringer-Ingelheim's donation of Viramune (nevirapine) for prevention of mother-to-child transmission of HIV in developing countries (Viramune Donation Programme, 2002), and the donation by Pfizer Inc. (decided after repeated protests by AIDS activists) of the antifungal Diflucan (fluconazole) for treatment of opportunistic infections (cryptococcal meningitis and esophageal candidiasis) in 12 African countries and Haiti (and more countries over time). In Botswana, Merck & Co. is working with the Bill and Melinda Gates Foundation and Government of Botswana to support the African Comprehensive HIV/AIDS Partnerships (ACHAP). Merck decided to invest US\$50 million over five years (along with US\$50 million from the Gates Foundation) and is providing Crixivan (indinavir) and Stocrin (efavirine) for the duration of the program.

Other pharmaceutical companies have made financial and product donations of various scales and in different geographic locations. Because donations are voluntary, these programs differ in their levels and duration of commitment. Whether significant donations of other AIDS medicines will occur in the future is uncertain. Some activists have opposed donation programs, because of questions about the continuity of supply for the long term and concerns that corporate donations are decided primarily for marketing reasons or tax benefits. They also argue that donations cannot provide a systemic solution to the great need for AIDS medicines in developing countries. Pharmaceutical company executives have disputed the charges about sustainability, marketing, and taxes; they have also responded that while donations cannot solve many of the problems of access, donations can make a positive contribution (Hardwick, 2001).

What the Future Holds

This chapter shows how the world made important progress in addressing the challenges that prices and patents posed to expanding global access to AIDS medicines. It demonstrates how major obstacles were recognized and removed through a contentious and iterative political process. The international regime of intellectual property rights was re-interpreted and re-negotiated to reduce its protection of high prices and its restrictions on generic production and exports. Research-based pharmaceutical companies and the international AIDS community altered standard business practices and pricing strategies in order to increase access to ARVs in the world's poorest countries. Prices for ARVs dropped precipitously in the developing world – in ways that few people expected. Pushed by activists, private companies and public agencies created a new potential for expanded global access to ARVs. Whether that potential will be achieved in practice remains to be seen; for millions around the world it is a case of too little too

Table 13.2 Seven key issues to be addressed in scaling-up access to ARVs.

1. Financing	Even at low prices, governments in developing countries lack sufficient funds
2. Procurement	Developing countries lack adequate procurement mechanisms for AIDS medicines
3. Infrastructure	Developing countries lack adequate health infrastructure in the public sector
4. Stigma and discrimination	Stigma and discrimination remain barriers to effective prevention, testing and treatment programs
5. Testing and diagnostics	There are a lack of testing facilities and low-cost diagnostics to support use of ARVs
6. Treatment protocols	The complexity of caring for AIDS patients remains a challenge
7. Operational experience	There is a lack of operational experience on the use of ARVs under field conditions

late. Cycles of price reduction will also be critical for new classes of ARVs, such as integrase inhibitors currently priced at US\$20 000 per patient per year.

Political pressure from many sources helped achieve these changes. Activist pressure on drug pricing and corporate images had a major impact. Indeed, one could persuasively argue that activist pressures shaped and pushed the policy agenda in ways that multinational companies never anticipated (and did not desire). But other pressures also contributed, especially the emerging competition from generic producers in Brazil and India along with a growing recognition inside pharmaceutical companies of their global social responsibilities (Roberts *et al.*, 2002).

But even with greatly reduced drug prices and a stronger global generic market, AIDS medicines remain out of reach for the majority of people in most developing countries. The dramatic decline in prices has highlighted persistent problems in the purchasing, procurement and distribution systems. These difficult problems, not directly related to drug cost, must be addressed to achieve equitable and sustained access to AIDS treatment in the world's poorest countries. The WHO's '3 by 5' Initiative is currently developing comprehensive plans for the components related to scaling-up access to ARVs. We have identified seven key issues that require attention (Table 13.2).

1. Financing

Governments lack adequate funds to purchase and deliver ARVs, even at low prices. Current prices offered in developing countries to treat one patient for a year are still much higher than the annual per capita GDP of many of the hardest hit countries (UNAIDS/WHO, 2003). The development of long-term financing

for AIDS treatment in developing countries remains a critical global priority. Developing country governments need to give higher priority to HIV/AIDS and mobilize existing and new resources to support national AIDS control strategies. Donor governments must also show more leadership to support responses to the epidemic through bilateral contributions and donations to international efforts such as the Global Fund to Fight AIDS, Tuberculosis and Malaria.

2. Procurement

Adequate mechanisms for ARV procurement do not currently exist. At present, each country is responsible for negotiating directly with individual companies on prices and conditions of procurement. This fragmented, market-based approach puts developing countries at disadvantage, because of limited information and market share. Initially, this approach was deliberately favored, as each national negotiation contributed to a further decline of prices. The situation is now different, because it is unlikely that prices will decline much further.

3. Infrastructure

The health infrastructure in many developing countries is inadequate to distribute and deliver ARVs safely and effectively to a significant portion of the infected population. In many poor countries, essential medicines do not reach people who need them, due to problems in financing, procurement, management, and delivery. Health centers and hospitals often lack adequate supplies of basic medicines, including antibiotics, antimalarials, and aspirin. Appropriate protocols for delivering ARVs will need to be designed and implemented in order to prevent the development of resistance. On the other hand, the business sector in developing countries often has private health facilities for employees and families and could play an important role in expanding access to treatment. To deliver ARVs in an effective and sustained way will require countries to improve the performance and equity of their health systems (Roberts *et al.*, 2004).

4. Stigma and Discrimination

Stigma and discrimination associated with HIV/AIDS are among the greatest barriers to the prevention of new infections and to expanded access to care, support, and treatment services that allow people living with HIV/AIDS to lead productive lives. Availability of treatment can help break down the stigma associated with people living with HIV/AIDS and encourage people to get tested and know their

status. A number of existing ARV treatment programs report a low uptake of available services – commonly attributed to stigma associated with the epidemic, potential discrimination from lack of confidentiality, lack of support services, and high cost of diagnostics. Stigma and discrimination should be addressed as part of any comprehensive ARV treatment program.

5. Testing and Availability of Diagnostics

The fight for increased access to ARVs has highlighted the need for appropriate and cost-effective diagnostic support. Prior to the provision of antiretroviral therapy, individuals must be tested for HIV and have access to low-cost monitoring services to determine when they are ready for treatment. Over the years there has been an increase in the availability of a varied range of diagnostics to support voluntary counseling and testing, but over 90 per cent of individuals living with HIV do not know their serostatus. New diagnostics are easy to use and require minimal investment in infrastructure and training beyond mechanisms to ensure confidentiality and adequate counseling to support client needs. Improved diagnostic support is also essential to monitor the progression of the disease when on or off ARV therapy.

6. Treatment Protocols

Even if ARVs and other drugs were made available, major barriers remain to their effective use. Selecting which patients to treat and when in the disease progression will remain difficult decisions with important ethical implications (Daniels, 2004). Deciding on the optimum treatment regimens will be challenging, given the dearth of clinical trials and experience in developing countries. Ensuring compliance and monitoring the effects of treatment and drug resistance will be problematic, because of the general lack of sophisticated monitoring tests (CD4 counts and viral load). In addition, we cannot predict the effects on the health system of treating large numbers of AIDS patients for long periods of time. Treatment for HIV/AIDS also needs to be designed and implemented not as a stand-alone program but as part of a comprehensive prevention and care program. Treatment can serve as an entry point to assure these other components are in place to sustain broader care and support programs.

7. Operational Experience

An important obstacle to expanded access to AIDS medicines is the lack of operational experience on how to use ARVs under field conditions in poor countries.

Even if the medicines were made available for free (either through donations or external financing), we need guidelines on how to use them. Recent experiences in Botswana may help provide some answers about best practices in the African context. In particular, we need to understand how to deliver AIDS treatment in the private sector – including mission hospitals, employer facilities, and private practitioners – where quality of services tends to be higher than in public facilities. In order to assure that expanded access does more good than harm, there is a need for increased capacity and training of medical professionals and more systematic evidence about what works and what does not in providing AIDS treatment in the least developed countries.

These seven challenges continue to delay access to ARVs (and other AIDS drugs) for the majority of HIV-infected people in most developing countries. Proposals that seek to expand access to AIDS medicines will need to resolve these problems, and also address issues related to the allocation of resources for competing health and development problems. The international AIDS community grappled with the problems of pricing and patents, and produced several mechanisms that have greatly reduced the obstacles to access. Similar efforts will be needed for the remaining problems noted above, in order to assure expanded global access to effective AIDS medicines for the majority of affected people who live in the world's poorest countries.

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