

# TRIPS post-2005 and access to new antiretroviral treatments in southern countries: issues and challenges

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## Introduction

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The year 2005 marked the end of the transitional period allowed developing countries to introduce the 'common minimum standards' of the Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS) into their national intellectual property laws. This worldwide upward harmonization, entailing legal recognition of the patentability of pharmaceutical products by all World Trade Organization (WTO) members, will greatly limit the development of low-cost generic versions of drugs, especially the most recent and innovative ones. This is particularly true in the field of HIV/AIDS, where the need for the more recently patented second-generation drugs used in antiretroviral therapy (ART) is already growing and is expected to increase significantly in southern countries [1].

Until 2005, some developing countries with pharmaceutical manufacturing capacities, especially India, used the transitional period allowing local manufacturers to produce and sell generic versions of first-generation ART drugs patented in industrialized countries and originally produced and sold at high prices by Western pharmaceutical companies [2,3]. Thanks to international competition between generic manufacturers and these companies,

significant price reductions were achieved for the large majority of these drugs. This was a key factor in the implementation and strengthening of access to AIDS treatment in developing countries, and a strategic element in the World Health Organization (WHO) '3by5' plan [4]. However, with the end of the extended deadline for TRIPS compliance, the scenario is likely to change radically.

Considering the end of the transitional period, which effectively will prohibit the free manufacture of newer and innovative antiretroviral generations, to mark a key episode in the history of the fight against AIDS in developing countries, this review will provide an overview of the meaning and consequences of this turning point and to present some of the new challenges of the post-2005 period.

## From the TRIPS to its 2005 amendment: restricted room for manoeuvre in generic competition

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Coming after the considerable strengthening of intellectual property rights in northern countries [5], the signing

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of the TRIPS in 1994 heralded the enforcement of this new, stricter patent regime on a worldwide scale [6]. By implementing so-called 'minimum standards', the new treaty insured a dramatic worldwide upward harmonization and marked a radical break with some of the foundations and rules that had hitherto shaped international intellectual property protection [7]. It introduced two main new 'minimum standards': (a) the patentability of therapeutic molecules became mandatory in all country members, and (b) the length of patent protection was extended to 20 years.

It should be remembered that, before the signing of the TRIPS, international treaties recognized the right of different countries to implement different systems of intellectual property protection, according to their level of economic development and the products concerned. Among these products, drugs, considered 'basic needs', were ranked of the highest importance [8]. This explains why, even in most developed countries, patents on therapeutic molecules were not introduced until the 1960s and sometimes much later. In Switzerland, for example, such patents were only introduced in 1977, enabling this country to build up a very powerful pharmaceutical industry largely founded on reverse engineering and the copying of existing molecules.

In most developing countries, the absence or laxity of a patent protection in pharmaceuticals prevailed until the mid-1990s. Exploiting their rights 'to learn by imitating' and 'copying', some developing countries established a large local industry for the low-cost production of generic drugs as a way to ensure access to treatment for the poorer segments of the population [9,10].

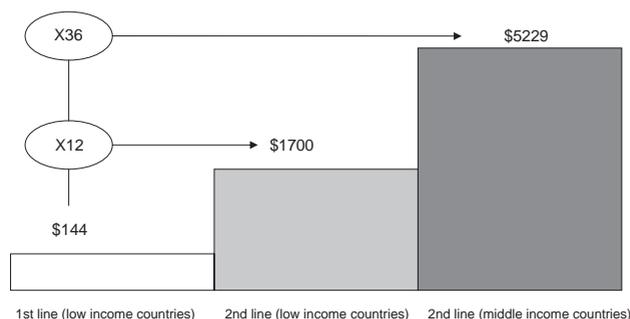
Although developing countries were given the deadline of 2005 for TRIPS compliance, few of them were able to resist the pressure exerted by developed countries to anticipate the date of compliance. India represents a notable exception, extensively using its right to copy existing molecules up until the end of the deadline (2005), thus playing a crucial role in the supply of generic first-line ART at reduced and affordable prices during the transitional period. It is thanks to the supply of generic versions of such drugs that some of the first-line therapies are now available at prices between US\$200 and 300 per person per year, compared with the US\$12 000–14 000 per person per year demanded by the patent holders before generic versions came into the international market [3].

It is also noteworthy that the most remarkable innovation (a turning point in the history of access to treatment in southern countries), the 'fixed dose combination' introduced first by the Indian company CIPLA, was possible only because this company (using the opportunity provided by Indian intellectual property law prevailing until 2005) could aggregate, in a single pill,

three ART drugs patented by different companies. This resulted in dramatic price reductions. The type of combination of drugs offered in this first-line fixed-dose triple therapy is available in 2007 for as little as US\$132 per patient per year and constitutes the most widespread first-line treatment in many developing countries [3].

Unfortunately, such price reductions cannot be envisaged for the new generation of ART drugs. With the end of the transitional period and the passing of the Indian Patent Amendments Act (voted in March 2005), the Indian generic drug manufacturers will now be forbidden to manufacture the new ART drugs [11]. In practice, dramatic effects will result from these changes. Generic equivalents of most second-generation ART drugs, especially those recommended in the second-line regimens, will not be available. In the context of increasing need for second-generation ART in developing countries, national budgets will not be able to sustain the cost of drugs in the short term without generic competition. Figure 1 illustrates this issue by comparing the median price paid in developing countries for the first-line combination (lamivudine, stavudine and nevirapine) with the price paid for one of the WHO-recommended second-line regimens (abacavir, didanosine and ritonavir-boosted lopinavir), according to the WHO Global Price Reporting Mechanism database [12].

Here, it is important to note the difference in prices paid in low- and middle-income countries for the second-line regimen. This results from the differential price policy practiced by originator companies in the context of their 'access programmes'. Most of these laboratories offer different prices for patented ART drugs depending on the countries to which they are sold, the lowest prices being granted only to the least-developed countries and sub-Saharan Africa. However, surveys conducted by Médecins Sans Frontières have shown that the variability in conditions of application from one laboratory to another, the absence of registration and marketing of certain ART



**Fig. 1.** Median price paid in 2005 by developing countries for second-line antiretroviral therapy (abacavir/didanosine/ritonavir-boosted lopinavir), compared with first-line regimen (lamivudine, stavudine and nevirapine) reported to the World Health Organization Global Price Reporting Mechanism [3,12].

in the eligible countries and the complexity of the distribution circuit chosen by the laboratories for their reduced-price products often make effective access to differential prices very difficult for the least-developed countries [3].

In other developing countries (not eligible for access programmes according to the conditions laid down by the originator companies), prices are negotiated on a case-by-case basis, generating very large price differences. According to WHO data, middle-income countries can pay as much as nine times more than the least-developed countries for recent ART drugs such as ritonavir-boosted lopinavir [12]. The price offered to least-developed countries by the company Abbott in its 'access program' for ritonavir-boosted lopinavir (Kaletra) is US\$500 per person per year. In Chile, the price was US\$4119 for a transaction carried out in September 2005, while in Brazil, after tough negotiations, the price was fixed at US\$1379 (see below).

From a legal point of view, generic versions of newly patented ART can still be manufactured, but only through the issuing of compulsory licences. Compulsory licensing is one of the exceptions to exclusive patent rights allowed by the TRIPS. This legal tool allows WTO members to authorize themselves or third parties to use the subject matter of a patent, without the permission of the patent holder, but with negotiated royalties. However, there are strict limitations to the issuing of such compulsory licences. In particular, article 31f of the TRIPS stipulates that such licences should be granted 'predominantly' to supply the 'domestic market'. A key consequence of these provisions is that it is almost impossible for countries lacking technological capabilities to use compulsory licences effectively. The contradiction here is at its highest, since article 31f entails that the poorest and most fragile countries (the ones lacking technological capabilities) are also the ones most unlikely to gain access to copies of patented drugs (through imports).

This situation and the more general criticisms leveled at the many unbalances of the TRIPS provisions [13] has provoked a vast debate on the relationship between TRIPS and access to drugs, leading to the adoption, at the *Fourth WTO Ministerial Conference* in Doha in 2001, of the famous *Doha Declaration on the TRIPS and Public Health* [14]. In this, ministers of WTO member countries recognized the serious public health problems raised by article 31f of the TRIPS for countries with little or no drug-manufacturing capacity and mandated the TRIPS Council to find an 'expeditious' solution to this problem.

It was only on August 2003, after bitter negotiations, that the WTO General Council adopted a so-called 'Decision' to implement paragraph 6 of the Doha

Declaration [15]. Later, in December 2005, this temporary Decision became permanent with the adoption of an amendment to the TRIPS [16].

The terms and conditions of the Decision are so rigid, however, that we are very unlikely to see the new drugs being effectively incorporated into treatments in southern countries.

## Where we stand: the post-2005 legal framework

Recognizing explicitly that for pharmaceutical products, exceptional circumstances justified the implementation of special means, the Decision defined a system to be followed by both the exporting and the importing country.

The most serious constraints imposed by the Decision are (a) the application of a double compulsory licence, which must be performed rigorously in the same terms in both the importing and the exporting country; and (b) the limitations imposed on the generic manufacturer, who must produce the exact amount requested by the importing country as specified in the compulsory licence [16,17].

Since the Decision stated that generic manufacturers are not allowed to produce any more than the quantities predefined in each compulsory licence, a powerful inbuilt mechanism is introduced to impede the large-scale production required to deliver the goods at low cost.

So it is hardly surprising that, to date, not one application of the Decision has been implemented. There is some evidence that the Amendment is not seen as an efficient solution or as the end of the debate on intellectual property and public health.

Moreover, a series of bilateral 'TRIPS Plus' agreements have been signed over the last few years, usually between southern countries and the United States. These bilateral agreements include several new provisions that reach far beyond the 'minimum standards' implemented by the TRIPS, calling into question the multilateral arrangements to address public health issues [18,19].

The proliferation of these bilateral agreements, as well as the rigidity of TRIPS amendments, clearly shows how the impact of intellectual property might threaten public health. This situation is unlikely to be solved in the short term.

The case of the Brazilian anti-AIDS programme deserves particular attention. It provides a unique case study of the contradictions raised by the enforcement of the TRIPS. It enables us to appreciate what has been possible within the

constraints of TRIPS, and the threats that this agreement and its recent developments now pose for the sustainability of national responses to the pandemic, even when the public health authorities are strongly committed to healthcare programmes, as are the Brazilian authorities.

## Challenges to sustainability within southern countries: the case of the Brazilian response

Since the mid-1990s, the Brazilian government has established a consistent legal framework to provide free and universal access to diagnosis, prevention and treatment for patients with HIV/AIDS [20].

At the end of 1990s, the Brazilian government, driven by resource constraints and facing the challenge posed by the very high prices of ART marketed by patent holders, launched a concerted action involving the Ministry of Health, the public pharmaceutical laboratories and the national pharmaceutical companies, aiming at the local manufacturing of generic versions of ART. This collaboration resulted in the national production of 10 low-cost generic versions of the nonpatented ART drugs listed in the national therapeutic guidelines [10,20].

In 2001, 56% of all ART consumed was nationally produced, resulting in a reduction of 82% in the purchase price of these drugs over the period from 1996 to 2001 [21]. At the same time, the Brazilian government conducted intense price negotiations with the pharmaceutical companies for patented ART drugs. At that time, the threat to use compulsory licensing proved a strong argument, notably owing to the know-how and technological capabilities acquired by the country through the local manufacturing of generic ART.

Yet, the early compliance of Brazil to the TRIPS (achieved as early as 1996) greatly hampered the public health policy to scale up patented ART. By not taking advantage of the 10-year transitional period for TRIPS compliance, the Brazilian government was obliged to amend its intellectual property legislation immediately to recognize pharmaceutical products and processes as patentable subject matters. Notwithstanding the implementation of some flexibilities allowed by TRIPS, the application of such provisions proved cumbersome and dependent upon more detailed legal definition. In 2006, of the 17 ART drugs currently used by the AIDS programme, 10 are patented or under patent application (Table 1)

### A more and more ineffective local industry faced with the evolution in treatments

Presently, there are 158 000 patients taking ART in Brazil, with an expected 15 000 new AIDS cases every year.

**Table 1. Initial therapy recommended in Brazil and patent status of antiretroviral drugs n 2006<sup>a</sup>.**

Preferential	2NRTI+1NNRTI	
Alternative	2NRTI + PI/r or PI	
Therapeutic class	First option	Second option
NRTI	AZT+3TC	ABC <sup>b</sup> + 3TC or ddl + 3TC or TDF <sup>c</sup> + 3TC
NNRTI	EFZ <sup>b</sup>	NVP
PI	LPV/r <sup>b</sup> or ATV/r <sup>b</sup>	ATV <sup>b</sup> or NFV or SQV/r <sup>b</sup>

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; AZT, zidovudine; 3TC, lamivudine; ddl, didanosine; ABC, abacavir; TDF, tenofovir DF; ATV, atazanavir; NFV, nelfinavir; /r, ritonavir boosting; SQV, saquinavir; NVP, nevirapine; EFZ, efavirenz

<sup>a</sup>Data from Coriat *et al.* [17] and the Brazilian Ministry of Health [22].

<sup>b</sup>Under patent.

<sup>c</sup>Under patent application.

Nevertheless, the sustainability of the Brazilian response to the epidemic is now facing new challenges to maintain the level of success achieved since the launch of the programme. First, the patent protection conferred by the TRIPS only permits local manufacturing of the oldest ART drugs. Moreover, because of insufficient national capability in the synthesis of molecules, most of the 'active pharmaceutical ingredients' used in the local production of nonpatented ART have been imported from China and India [10]. This represents a serious threat to the future of the AIDS programme. By reducing sources of cheap chemical inputs, the TRIPS compliance of these major suppliers of active pharmaceutical ingredients may jeopardize the procurement policy and the whole architecture on which the Brazilian programme is based.

Second, most of the latest generations of ART (entirely protected by patents) has to be imported. These imports are likely to grow fast in the future, as the trends on therapeutic guidelines point to the inclusion of newer generation ART drugs as substitutes for older ones. Such is the case for tenofovir, indicated as a preferential drug in the early stages of treatment. Similarly, new regimens for a growing number of patients include ritonavir-boosted lopinavir and atazanavir as alternatives to older drugs of the same therapeutic class (Table 1).

This situation has led to an acute imbalance in national budget expenditure for ART procurement in Brazil. Approximately 80% of the Ministry of Health's budget is currently spent in the procurement of imported patented drugs. Almost 65% of this budget is devoted to the acquisition of ritonavir-boosted lopinavir (34.5%), efavirenz (17.8%) and tenofovir (12.2%). According to Ministry of Health estimates, spending on these three drugs might increase two-fold by 2011 [23].

The impossibility of using local production, thus exerting competitive pressure through new generic ART, has

yielded weaker commitments and agreements on price negotiation. One example is the supply agreement established with Abbott for Kaletra in 2005.

### **Losing bargaining power over the strategic new molecules: the 'Kaletra case'**

The case of Kaletra provides a perfect illustration of the new post-2005 situation and the difficulties it raises. Since its introduction into the therapeutic guidelines in 2002, Kaletra has occupied an increasingly important place in Brazilian treatment regimens, gradually replacing nelfinavir and indinavir.

The purchase of Kaletra represents the biggest share of the ART procurement budget. This explains why a series of initiatives involving the patent owner Abbott, governmental institutions and the Civil Society were taken, aiming at issuing a compulsory licence.

After the publication of the so-called 'Administrative Ruling on Public Interest' for the antiretroviral Kaletra – final step before the issuing of a compulsory licence – the Brazilian government experienced severe pressure from the pharmaceutical company. This situation generated an internal conflict amongst the different national authorities, between those arguing for the compulsory licence and those arguing for renegotiation with the pharmaceutical company.

Finally, an agreement with Abbott was signed in October 2005. Although providing short-term benefits – particularly a reduction of 46% in the unit price of soft gelatin capsules (from US\$1.17 to US\$0.63) and the prompt introduction of a new, reduced daily-dose formulation (Meltrex) – the agreement also contained various negative provisions. The main restrictive provisions of the agreement are as follows:

1. The Brazilian Ministry of Health committed itself not to exploit potential flexibilities in Abbott's intellectual property for any formulation including lopinavir and ritonavir, until 2011. Such a provision is considered 'TRIPS Plus', since its scope extends beyond the pharmaceutical product Kaletra to include all possible combinations of its two compounds.
2. The fixing of the price of Meltrex until the expiry of the agreement. By fixing the price of Meltrex at US\$1.04 until 2011, the agreement represents a considerable loss of opportunity, as the Brazilian Ministry of Health cannot benefit from natural price reduction trends over this period.
3. The early introduction of the Meltrex formulation in the first stages of treatment as a substitute for the soft-capsule formulation. This will considerably burden the Ministry of Health's budget over the mid to long term, as Meltrex is twice the price of the soft gelatin formulation.

The case of tenofovir, currently the subject of pre-grant opposition (in Brazil, but also in India) provides another illustration of the new complexity and difficulties faced by southern countries in procuring the most recent ART.

### **Should the manufacturing of generic antiretroviral drugs be halted? The pre-grant opposition to the tenofovir patent application**

Brazilian law, like the Indian law of 2005, provides for the possibility of using a procedure called 'pre-grant opposition', which allows any interested party to submit subsidiary information to the local Patent Office during the examination of a patent application. The aim of this mechanism is to prove that the application subject matter does not comply with one or more of the traditional patentability criteria: novelty, inventive step (nonobviousness) and industrial applicability (usefulness).

Currently, the Patent Offices of India and Brazil have received technical reports stating that the patent application for tenofovir does not meet the inventive step criterion. In Brazil, Far-manguinhos, the state-run Institute of Pharmaceutical Technology, is also at the origin of the pre-grant opposition.

The issue at stake is whether generic manufacturers of tenofovir, such as the Indian pharmaceutical company Cipla, will have to stop their production of this drug. According to Médecins sans Frontière, the generic version of tenofovir is actually sold by Cipla at US\$973 per patient per year and at US\$365 by Heterodrugs, another Indian firm [3]. In Brazil, tenofovir is actually sold by Gilead at US\$1387 per patient per year [22].

It is important to note that India's patent law is currently subject to legal proceedings, initiated by the Swiss pharmaceutical company Novartis on the grounds that its 'pre-grant opposition' section is anticonstitutional and not compliant with the TRIPS. These proceedings, brought before the Indian High Court, follow the rejection by the Indian Patent Office of Novartis's patent application for the cancer drug Gleevec (imatinib mesylate) in January 2006, after 'pre-grant opposition' filed by a number of Indian patients' groups [24].

### **Conclusion: towards a health paradox?**

As we hope to have shown, the end of the transitional period for TRIPS compliance heralds a highly uncertain

and risky situation for developing countries. The major threat is to the procurement of drugs at reduced prices, especially the new generation of drugs. This is the case for tenofovir, recently recommended by the WHO for first-line treatments in resource-limited settings, and for ritonavir-boosted lopinavir, the key element in the construction of an effective second-line regimen [1].

The enforcement of intellectual property rules imposed by the end of the transition period is thus generating a 'health paradox': at a time when everything should be organized to favour access to new medicines for poorer countries, the new intellectual property rules coming into force make this access more unlikely than ever. Already, several of the poorest countries cannot supply those patients who need certain drugs.

The policy of differential prices adopted by the originator companies in their access programmes can no doubt play a significant role in the access to new generations of drugs in developing countries. However, the current conditions of eligibility and the complexity of these programmes do not appear to encourage an objective of wide access to ART. Furthermore, the absence of competition from generic drugs for recent ART suggests that price falls will be far less significant than they were for the first generation of ART. Lastly, the supply of patented specialties at reduced prices has the disadvantage of being highly unpredictable (in terms of both products and prices). It depends on the 'goodwill' of the laboratories (or on their market-penetration strategies), when the treatments and patients need security, predictability and stability.

After the first modest but real successes achieved recently, will current efforts towards scaling up be compromised by the paradox created by the end of the transition period? If urgent action is not taken to make the new generation of drugs affordable in southern countries, there is a strong risk that many countries will be restricted to inaccurate and ineffective treatments.

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