BACKGROUND: ACCESS TO ANTIRETROVIRALS

TREAT AIDS: SAVE LIVES, STOP THE VIRUS

At the United Nations High Level Meeting on AIDS in New York in June 2011, governments committed to reaching 15 million people with HIV treatment by 2015 – nearly nine million more than are on treatment today.[1]

New data adds to a growing body of evidence that as well as saving lives, treating HIV can also help prevent HIV transmission, making the scale-up of treatment all the more urgent. In May 2011, a study called HPTN 052 supported by the US National Institutes of Health found a 96% reduction in transmission when HIV-positive persons in a relationship with an HIV-negative person were started early on antiretroviral therapy compared to people whose treatment was deferred.[2] Early treatment also significantly reduced the development of tuberculosis, which remains the number one killer of people living with HIV/AIDS.

If HIV treatment and prevention interventions are ambitiously expanded, according to UNAIDS, twelve million infections and more than seven million deaths can be averted by 2020. The number of new infections could be reduced by more than half by 2015.[ii]

In order to reach such a target, countries need to commit significant financial resources to the epidemic – an additional US$ 6 billion annual top up by 2015.[ii] However, funding for AIDS declined in both 2009 and 2010, leaving the Global Fund to Fight AIDS, TB and Malaria, the US government's PEPFAR and national programmes short of resources.

Countries will also need to ensure that the medicines needed to break the back of the epidemic remain affordable. And here, the following challenges need to be addressed:

- Ensuring access to improved first-line treatment options
- Ensuring access to treatment options for second-line and beyond
- Ensuring generic production and reining in drug costs


© Sven Torfinn

Médecins Sans Frontières (MSF) began providing antiretroviral treatment (ART) for HIV/AIDS in 2000 in Thailand, Cameroon and South Africa, to a limited number of people living with HIV/AIDS in urgent need of treatment.[3] Today, MSF treats more than 170,000 people in 19 countries, and some MSF projects have been able to reach and maintain 'universal access' to treatment in their districts.[i]

The past ten years have been rich in lessons learnt: how bringing treatment to primary health centres and rural clinics, closer to where people lives, means more people can be reached with care; how simplified patient-friendly treatment, with several medicines combined into one pill, facilitates adherence and improves results; how providing treatment for HIV and TB under the same roof by the same health worker reduces the burden on patients; and how tasks can be shifted, so that nurses can perform many of the duties previously reserved for doctors to overcome health worker shortages. For more details on these and other issues on HIV/AIDS treatment, read MSF's May 2011 report *Getting Ahead of the Wave: Lessons for the Next Decade of the AIDS Response*.[ii]

[i] Defined as reaching 80% of people in need of HIV/AIDS treatment.

[ii] Available in English, French, Spanish and Portuguese.

ENSURING ACCESS TO IMPROVED FIRST-LINE TREATMENT OPTIONS

Today, the majority of people on first-line of ARVs in low- and middle-income countries receive the combination of lamivudine/stavudine/nevirapine (3TC/d4T/NVP).[4] Thanks to generic competition, this regimen now costs $61 per patient per year (ppy).

Stavudine (d4T) has played a crucial role in ART scale-up in resource-limited settings, due to its availability in fixed-dose combinations and, most significantly its low cost. But despite its affordability, using this standard combination comes at a medical cost for some patients. Stavudine causes serious side effects, some intolerable (peripheral neuropathy), stigmatising (lipodystrophy) and potentially life-threatening (lactic acidosis). For these reasons, stavudine is virtually no longer used in wealthy countries (in 2006, for example, fewer than 2% of patients in Switzerland were taking the drug),[5] where patients are offered better-tolerated alternatives, such as tenofovir (TDF).

Since 2006, WHO has recommended in its HIV/AIDS treatment guidelines that treatment providers begin moving away from d4T because of its long-term irreversible side effects, towards TDF or zidovudine (AZT).[6] This call was repeated in the latest guidelines released by WHO in 2010,[7] with a clear recommendation to phase out d4T. In February 2011, the European Medicines Agency recommended that, in view of its long-term toxicities, d4T be used for as short a time as possible and only when no appropriate alternatives exist.[8]

But until now, the higher cost of these alternatives has largely prevented this switch in many developing countries. Better-tolerated first-line regimens are still at best more than double the price of the d4T-based first-line regimen.

The price of treatment is clearly a critical concern. But the long-term benefits of people being able to tolerate and stay on their first ARV combination longer can outweigh the costs. As one of the main reasons people stop adhering to their treatment is side effects, using medicines with fewer side effects can also improve adherence, and delay the need to switch to a much more expensive second-line regimen because of resistance. A study by MSF in Lesotho showed that people taking TDF were almost six times less likely to have to switch regimens compared to those taking d4T and twice less likely than AZT.[10] It is therefore critical that treatment providers move away from d4T as has been done for example in Zambia, Lesotho, Guyana, South Africa and Botswana. A survey conducted in 16 countries where MSF works showed that seven had changed their protocols to provide all new patients with better-tolerated ARVs.[10] This is encouraging news, but some countries have been prevented from making the switch because of funding constraints.

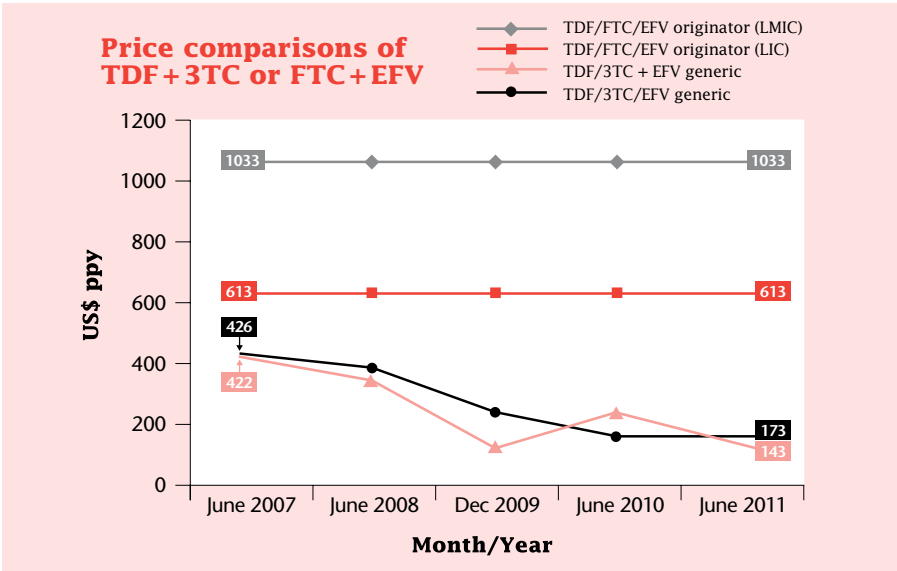
In the price analysis for this edition we found a noteworthy downward trend in the prices of improved (tenofovir-based) first-line combinations, and prices can be expected to fall further as demand increases. In countries where the drugs are not under patent or where patents owners permit generic competition, the one-pill-once-a-day generic triple combination containing tenofovir/lamivudine/efavirenz (TDF/3TC/EFV) is now available for $173 ppy **(see graph 1)**.

But in some lower middle-income countries, patents prevent access to generic products, meaning that countries have to rely on the 'discounted' price offered by originator companies – $1,033 ppy for tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV), nearly six times the cost of the alternative equivalent generic version.

Companies are increasingly excluding middle-income countries from even these offers of discounted prices, however.[iii] ViiV considers Global Fund-financed programmes in middle-income countries to be ineligible for discounted prices, which will have to negotiate prices on a case-by-case basis. Merck has ceased to offer standardised price discounts to all lower middle- and upper middle-income countries. Abbott specifically excludes lower middle-income and low-income countries outside of Africa from standardised price discounts for the heat-stable ritonavir 100mg tablet. Tibotec/Johnson & Johnson are also excluding all middle-income countries from standardised price discounts for all their ARVs.

GRAPH 1: PATENTS AS A BARRIER TO IMPROVED TREATMENT.

As demand has increased, the price of improved first-line regimens has fallen considerably for countries where the absence of patent barriers means the generic versions can be accessed. Lower middle-income countries (LMIC) unable to access the generic price have not benefitted.



[iii] Least-developed countries, low-income countries, middle-income countries, etc: each pharmaceutical company defines its own eligibility criteria to assess which country is entitled to price discounts. Please consult the Untangling the Web annexes for details about individual companies' differential pricing schemes.

ENSURING ACCESS TO TREATMENT OPTIONS FOR SECOND-LINE AND BEYOND

Sustaining HIV treatment over the long-term requires continued access to effective treatments such that patients who develop side-effects or drug resistance, or have to take medications that adversely interact with certain antiretroviral drugs, are able to switch to other antiretrovirals. With growing numbers of patients in developing countries having been on treatment for a number of years, ensuring the effectiveness of treatment as well as their long-term survival depends on access to newer and more potent drugs when they inevitably develop resistance to their medicines over time.

In one of MSF's longest-running HIV/AIDS treatment programmes, in Khayelitsha, South Africa, 12.2%[11] of patients on treatment for five years needed to switch to a second-line drug combination because of virological failure. As some patients in developing countries will inevitably require treatment options beyond their second-line regimen, it is crucial to secure further treatment options to ensure long-term treatment success for all patients.

MSF's Khayelitsha data provide a window into the growing need for access to newer HIV/AIDS drug regimens across the developing world in the coming years. Demand for newer AIDS drugs is growing fast – it is estimated that the need for second-line medicines will reach almost half a million by 2012.[13]

However, the price of newer medicines remains a major barrier to access.

The second-line regimen with zidovudine and atazanavir recommended by WHO is today priced at $442 **(see graph 2)**. Although price has come down, this is still three times more than the TDF-based first-line regimen recommended by WHO.

In its 2010 treatment guidelines, WHO for the first time raised the need for treatment options after potential failure of second-line therapy. Many studies are ongoing, and the drugs likely to have anti-HIV activity in third-line regimens are raltegravir, darunavir (boosted with ritonavir), and etravirine.[7]

TREATMENT FAILURE UNDER-DIAGNOSED

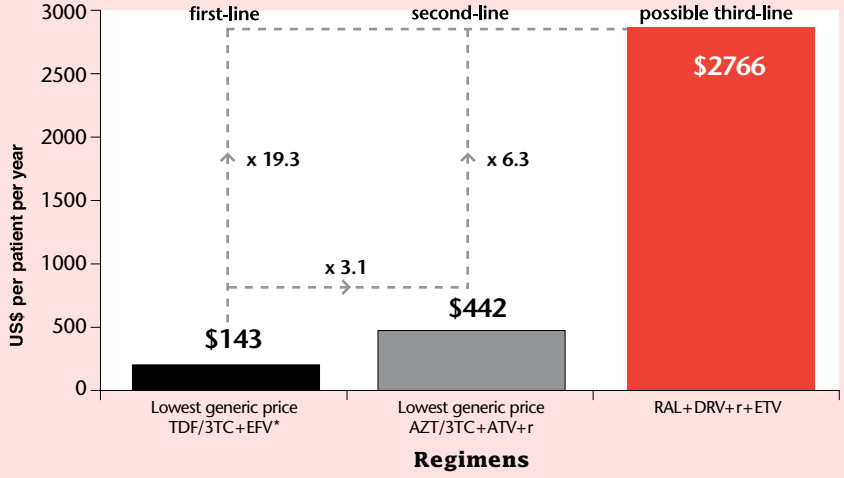
The routine, six-monthly, measurement of viral load is a WHO-recommended diagnostic tool for monitoring all HIV positive patients on ART.[6] The use of routine viral load monitoring can successfully diagnose treatment failure early enough to prevent the development of drug resistance through adherence counselling.

Viral load testing is crucially important for deciding when it is necessary to switch a patient to expensive second-line drugs.[19, 21, 46] Unfortunately, due to the high cost and complexity of the currently available laboratory-based tests, viral load monitoring is not widely implemented in resource-limited settings; with the consequence that treatment failure is largely under-diagnosed.[100]

GRAPH 2: THE TREATMENT TIME BOMB: THE IMPACT ON THE PRICE OF ARV TREATMENT OF SWITCHING TO SECOND-LINE REGIMENS AND BEYOND.

Changing a patient's regimen because of the emergence of resistance means relying on newer, patented, and therefore more expensive drugs. The price of a possible third-line regimen is close to 20 times more than the most affordable WHO recommended first-line regimen, and over six times more than the most affordable second-line regimen. Patients and treatment providers are once again faced with the prospect of drugs being priced out of reach.

Price comparisons of first-line, second-line and possible third-line



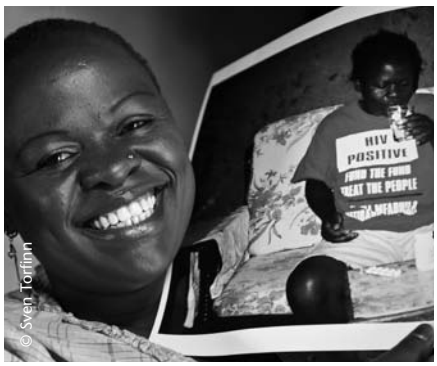
*Although a quality-assured generic TDF/3TC/EFV fixed-dose combination exists (and as one pill once a day is better suited for use in resource-limited settings that a TDF/3TC + EFV co-pack), its price ($173) remains higher than the co-pack ($143), in the absence of competition from further manufacturers.

Continued overleaf

Because of patent barriers, there is no generic version for either etravirine, darunavir or raltegravir, and company price discounts are not affordable for developing countries. Tibotec / Johnson & Johnson, who manufactures etravirine and darunavir, has announced 'discounted' prices for sub-Saharan Africa and least-developed countries, at $913 and $1,095 ppy, respectively. Raltegravir is also widely patented, and its manufacturer, Merck, has ceased giving standardised price discounts to lower middle-income countries.

Without generic competition to bring prices down, a potential third-line regimen could thus be available for the poorest countries for the prohibitive price of $2,766 ppy, at best. This price applies to Africa and least-developed countries only, with middle-income countries again paying substantially more. In Brazil, for example, the cost of raltegravir reaches $5,870 ppy, and darunavir (boosted with ritonavir), costs over $6,000 ppy.

There is no room for complacency about these prices. For those people already failing on their second-line combination, this unaffordable price will mean they almost certainly once again face death.



© Sven Torfinn

INNOVATIONS: LOOKING TO THE PIPELINE

There are promising new drugs for the treatment of HIV in the future, including new classes of drugs that have new ways of preventing the virus from replicating. Some have the potential to be administered as long-acting formulations that would allow once-weekly or once-monthly dosing. And some of the drugs could be potentially cheaper than the ARVs most commonly used today.

Rilpivirine, for example, received US FDA approval in 2011. Rilpivirine has a number of disadvantages, but one major advantage for resource-limited settings is the fact that it can be produced for as little as $10 per patient per year[14] – and its potential for use in long-acting formulations – an injectable nano-suspension of rilpivirine has been developed and showed promise for monthly dosing.[14] More research is needed however to determine the safety and efficacy of higher doses.

In 2010, Tibotec (a subsidiary of Johnson & Johnson) signed agreements with generic producers to manufacture, market and distribute rilpivirine. These licences exclude many developing countries where Tibotec / Johnson & Johnson will likely charge high prices. All of Latin America, Central Asia and most Caribbean and South East Asian countries will not be able to access generic versions of the medicine.

Dolutegravir, from the new integrase inhibitor class, has been shown to be very potent at low doses, which suggests it could be produced at a low cost.[15] S/GSK1265744, also an integrase inhibitor, is being developed as a long-acting injectable. Other drugs also hold potential for long-acting formulation, like elvucitabine and CMX157. Thanks to long-acting formulations, some of these drugs might be more effective or durable than the ARVs we use in first-line today.

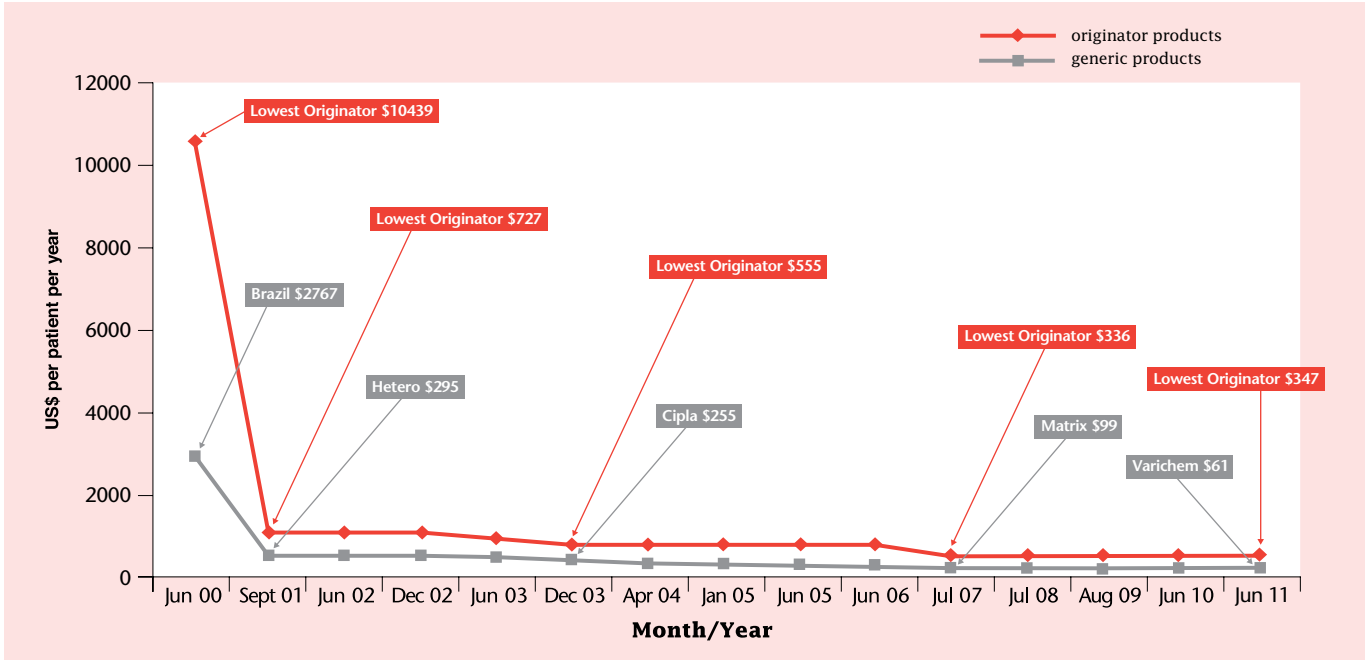
Ensuring access to promising drugs in the development pipeline, so that people in developing countries can benefit from therapeutic advances, will require surmounting patent barriers that prevent access.

ENSURING GENERIC PRODUCTION AND REINING IN DRUG COSTS

Competition among multiple generic pharmaceutical manufacturers in countries where medicines were not patented, especially India, is what brought the cost of HIV/AIDS treatment down by 99% over the past decade **(see graph 3)**. India has thus been called the 'pharmacy of the developing world': more than 80% of donor-funded purchases of ARVs for use in developing countries from 2003 to 2008 were manufactured in India, and more than 80% of the ARVs MSF uses are sourced from India.[16]

The lack of patents in India additionally allowed for the production of fixed-dose combination (FDC) pills, which is both supportive of patient adherence and crucial to the simplification of treatment that has been central to global scale-up of treatment.


© Bruno De Cock



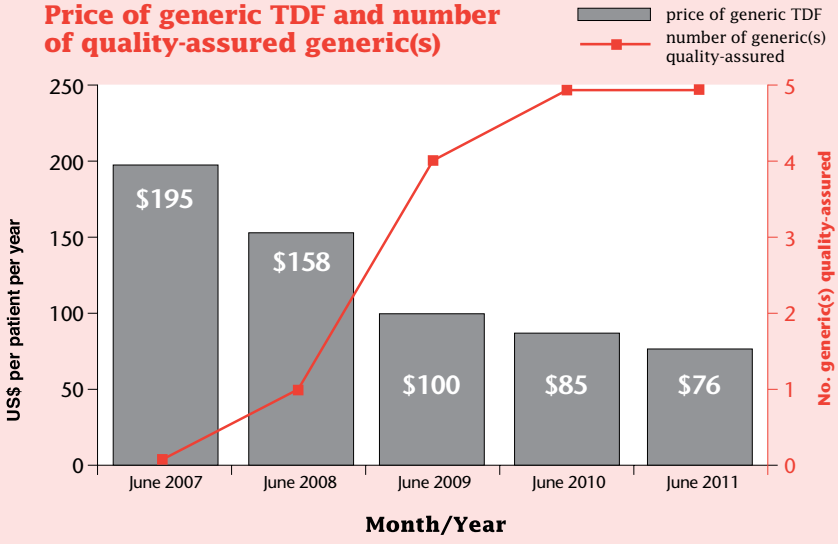
GRAPH 3: GENERIC COMPETITION AS A CATALYST FOR PRICE REDUCTIONS.

The fall in the price of first-line combination of stavudine (d4T), lamivudine (3TC), and nevirapine (NVP), since 2000.

Prices fall as the number of generic competitors increases – securing generic competition has therefore been essential to bringing the cost of drugs down to affordable levels **(see graph 4)**.

But increased product patenting in developing countries threatens the production of affordable generic versions of newer medicines and the development of new FDCs. International trade rules now require the patenting of medicines in key producing countries like India and Brazil, essentially blocking the kind of generic competition for the future that brought prices down so substantially in the past.

If stricter patent laws and other intellectual property measures mean that generic competition from India cannot act as a catalyst to bring down the prices of medicines, tomorrow's battle for access to affordable ARVs will need to be fought in a different way.



GRAPH 4: PRICES FALL AS MORE COMPETITORS ENTER THE MARKET.

DIFFERENTIAL PRICES, COMPULSORY LICENCES, VOLUNTARY LICENCES: WHAT SOLUTIONS FOR ACCESS?

Company-led access schemes have proven to be minimally effective. Primarily, the threat of losing a patent or having a patent barrier removed is what makes companies respond and reduce prices.

When drugs are patented, and pharmaceutical companies fail to make patented medicines available and affordable to patients in developing countries, governments should therefore make use of their right, under international trade laws, to issue compulsory licences (CLs) to ensure generic competition. CLs are one of the public health safeguards enshrined in the TRIPS Agreement, which allows a government to

Continued overleaf

Differential prices, compulsory licences, voluntary licences: what solutions for access? continued

override a patent by issuing a licence to a third party to produce or import the drug. CLs have proven to bring prices down dramatically by opening up the market to competition and thereby increasing access.

Alternatively, a patent holder can choose to grant voluntary licences (VL) to other manufacturers, allowing them to produce and export the drug in exchange for royalty payments. When these VLs are offered to multiple producers within a market or in several countries and are not restrictive in terms of where the licensees are allowed to export the drug, they can be a useful way to increase access.

However, restrictive VLs can also serve merely to extend the originator company's control over a given market, stipulating conditions such as which source the active ingredient must be purchased from, as well as to which countries the drugs can be exported. Such restrictive VLs ultimately do not lead to the unhindered competition that allows patients to benefit from the lowest prices possible, nor do they increase access in all countries where the medicines are needed.

The Medicines Patent Pool, established in 2010, is a voluntary mechanism whereby companies, researchers or universities license the patents on their inventions to one entity – the Pool. Any company that wants to use the patented inventions can seek a licence from the pool, in exchange for the payment of royalties to the patent holder. The licensee could then produce generic versions of the patented inventions and export them to countries covered by the licence.

The Pool could facilitate the production of cheaper medicines for developing countries, and to allow the production of needed fixed-dose combinations that would otherwise require lengthy negotiations with numerous different patent holders. It is important that future licences be public health-driven; meet the health needs of people living with HIV/AIDS in developing countries and do not contain restrictive or anti-competitive terms that limit competition and sources of manufacturing and distribution of the active pharmaceutical ingredient and final products.

Ensuring newer and better medicines are made affordable for people in developing countries means supporting policies to ensure generic competition and drive down prices, as well as refraining from pushing policies that prevent price-busting competition by imposing even greater intellectual property protection.

Supporting the policies needed to ensure generic competition and contain the cost of drugs is a political choice – one that countries have committed to at the UN since 2001 and re-iterated in the 2011 UN High Level Meeting on HIV/AIDS Declaration. Access to HIV medicines will depend on:

- Least-developed countries using their right not to grant or enforce medicines patents until 2016, and members of the World Trade Organization extending this deadline beyond 2016. This period expires in barely five years, and if it is not extended LDCs that have not already introduced product patent protection will then face the same patent barriers that other developing countries are already struggling with.
- Developing countries exercising their right to issue 'compulsory licences' to allow for production of more affordable generics; like Thailand in 2007, in a move which brought the price of lopinavir/ritonavir down by 75%, or Brazil, which overcame a patent on efavirenz in the same year, thereby enabling the government to import a generic version from India at one third of the originator company price, or Ecuador in 2010 which thereby halved the cost of lopinavir/ritonavir to the public health system.
- Developing countries designing flexible patent laws that favour access to medicines. India's patent law contains key health safeguards, reserving monopoly status only for those drugs that show a therapeutic benefit over ones that already exist – this restricts frivolous patenting and evergreening. The law also allows any interested party to oppose a patent before or after it is granted ('pre-grant' and 'post-grant' oppositions) so undeserved patents can be challenged. The use of these safeguards in the Indian law has resulted in the withdrawal of the patent application on lamivudine/zidovudine and the rejection of key patent applications on tenofovir, darunavir, nevirapine syrup and lopinavir/ritonavir allowing Indian generic companies to continue to manufacture, supply and export of these AIDS medicines to the rest of the developing world.
- World Trade Organization members reviewing and reforming the August 30 Decision, designed to allow the exporting and importing of medicines under a compulsory licence to countries which have no manufacturing capacity and cannot produce their own generic medicines. The experience of the only use of this flexibility in Canada has shown that what was intended to be an 'expeditious solution' fails to meet the needs of developing countries with no or insufficient manufacturing capacity to import medicines patented in drug-producing countries.[324]
- Developed countries immediately stopping to push measures – like data exclusivity, patent term extensions, enforcement measures and investment measures – that go beyond TRIPS in trade agreements. The European Union and the European Free Trade Association countries are currently pushing for policies to be included in trade deals with India that will further restrain competition and directly damage access to affordable medicines,

for example. By attacking the 'pharmacy of the developing world', such policies also directly undermine any effort by donor governments to finance and support treatment scale up. The United States' Special 301 mechanism is another example of a bilateral punitive measure to challenge efforts by developing countries to ensure access to medicines for their populations, and to drive countries to implement intellectual property measures into their domestic laws above those required by international trade law.

- All countries refraining from introducing intellectual property enforcement measures that limit the production, export, transit and importation of generic medicines, such as the Anti-Counterfeiting Trade Agreement (ACTA), as well as laws and measures that conflate legitimate generic medicines with deliberately falsified medicines under the term 'counterfeit', such as the Kenya Anti-Counterfeit Act of 2008.
- Pharmaceutical companies pursuing voluntary methods that enable generic competition in a way that meets the needs of people in developing countries and keep costs down. MSF is urging all entities that hold patents on HIV drugs to share their patents through the Medicines Patent Pool. The Pool could help overcome intellectual property hurdles, with a major impact if the licences cover all developing countries.

FREE TRADE AGREEMENTS: HANDS OFF OUR MEDICINE!

In 2010, MSF launched the *HANDS OFF* campaign to call on the European Union (EU) to drop the policies harmful to access to medicines being pushed as a part of the EU-India free trade agreement (FTA). In March 2011, around 4,000 people from across Asia living with HIV/AIDS and other life-threatening diseases marched in the streets of New Delhi to protest the impact the FTA could have on access to affordable medicines.

MSF and other treatment providers depend on a sustainable flow of affordable generics from India to treat people across the developing world – MSF sources more than 80% of the HIV medicines it uses to treat more than 170,000 people living with HIV/AIDS from manufacturers of generics in India. But this access is under threat, as the EU pushes measures – like data exclusivity, intellectual property enforcement measures and investment measures – that threaten to block the generic production of medicines.

These measures – and other free trade agreements, bilateral and multilateral initiatives that restrict access to medicines – undermine past successes in putting millions of people on treatment, and endanger future scale up of treatment.

Join the campaign.
Visit *action.msf.org*

HIGHLIGHTS FROM THE 14TH EDITION OF UNTANGLING THE WEB OF ANTIRETROVIRAL PRICES

Pharmaceutical companies are charging very high prices in middle-income countries.

- Middle-income countries pay high prices for AIDS medicines. The cost of the improved first-line containing tenofovir costs over $1000 for a year's treatment, almost six times more than in countries where the generic can be purchased. Newer treatment options fetch extremely high prices, with Brazil paying $5,870 for raltegravir, and over $6,000 for darunavir (boosted with ritonavir).
- Pharmaceutical companies are also actively excluding middle-income countries from accessing standardised price discounts. These moves are concerning for access to medicines in middle-income countries as case-by-case negotiations are likely to lead to higher prices:
- **ViiV** has clarified that their standardised price discounts were not in fact available to all fully-financed Global Fund or PEPFAR programmes, contrary to previous announcements. Global Fund-financed programmes in middle-income countries have not been and will not be eligible for these prices, and will have to negotiate prices with the company on a case-by-case basis.
- **Merck** ceased to offer standardised price discounts to all lower middle- and upper middle-income countries. The company proposes instead to negotiate discounted prices on a case-by-case basis, based on country income and disease burden. This is of great concern for the affordability of products and sustainability of government treatment programmes, especially given that Merck's previous pricing strategy (published in previous editions of Untangling the Web) was to offer middle-income countries prices that were up to more than ten times the price of generic versions. The price of raltegravir is of particular concern, given the extremely high prices charged in wealthy countries, at $8,000 ppy.

Continued overleaf

Highlights from the 14th edition of Untangling the Web of Antiretroviral Prices continued

- Although **Abbott** offers two tiers of standardised price discounts for the heat-stable fixed-dose combination of lopinavir/ritonavir, (with one price offered to all African countries and all least-developed countries outside Africa, and another to other low-income and lower middle-income economies), Abbott specifically excludes low-income and lower middle-income economies from standardised price discounts for the standalone heat-stable ritonavir 100mg tablet.
- **Tibotec / Johnson & Johnson** also exclude all middle-income countries from standardised price discounts for all their ARVs – including promising new drugs such as rilpivirine, as well as darunavir and etravirine (both important drugs for treatment-experienced patients that have been listed in WHO treatment guidelines as potential components of a salvage regimen).

The price of tenofovir (TDF) continues to fall, but the price of fixed-dose combinations containing TDF hamper treatment scale-up.

- Thanks to an increase in purchase volumes and to a new synthesis process which reduces the price of the active pharmaceutical ingredient, the price of one year's treatment with quality-assured generic TDF by itself now stands at $76. This compares with a lowest price of $88 for zidovudine (AZT), the second drug recommended by WHO for first-line treatment to replace stavudine (d4T).
- This should encourage countries to follow WHO recommendations and move away from d4T-based first-line regimens in favour of TDF-based regimens.
- TDF-containing first-line regimens such as TDF/3TC/EFV, TDF/FTC/EFV, (both of which are one pill, once a day) or TDF/3TC + NVP are very efficient and much better tolerated than d4T-based and AZT-based regimens. But their higher price forms a barrier to scale up of better treatment in some countries with funding constraints. TDF/FTC/EFV is a patented combination in many developing countries, with originator companies charging at best $613 for a year's treatment ($1033 in middle-income countries). Only one generic producer of three-in-one TDF/3TC/EFV is quality-assured by US FDA or WHO prequalification, and in the absence of competition, there has been little downward movement of the price, which is just $6 less than last year, at $173 ppy.
- While these prices are still higher than those for a d4T-based regimen, there is a need to generate greater demand for TDF which will, in turn, increase the competition and the economies of scale needed to further decrease prices.
- Countries like India and Brazil have used strict patentability criteria to ensure that new forms of tenofovir remain off-patent. Still, multiple pending patent applications on TDF and TDF-based combinations continue to threaten the future of generic competition for these medicines.

Children continue to be an afterthought.

- With the virtual elimination of paediatric AIDS in the developed world, research on paediatric formulations is not a priority for pharmaceutical companies. Despite the lack of a lucrative market in the developing world, patents on newer medicines are nevertheless hampering the creation of paediatric versions.
- Of the 23 antiretrovirals approved by the US FDA today, five are not approved for use in children, and seven do not come in any paediatric formulations.
- There is a need for studies in children to be conducted to ensure that further treatment options exist. New drugs such as raltegravir and etravirine are still lacking paediatric indication.
- There is a need to harmonise adult and paediatric regimens in order to simplify treatment and ensure treatment options are available for children as they grow into young adults. But tenofovir is still lacking an indication for children below 12 years of age. Gilead's Phase II trial involving children (aged between two and 12 years), using an oral powder formulation is still on-going. Such data, provided appropriate formulations are developed, will be crucial to address the urgent needs of this paediatric population.
- The absence of dosing studies for efavirenz in children below 3 years of age remains a problem for TB/HIV co-infected infants, for whom no adequate solution therefore exists to the problem of nevirapine interacting with anti-tuberculosis medicines.
- The lack of adapted formulations also acts as a barrier. The most commonly used protease inhibitor for the youngest children, a LPV/r solution, is not palatable and not adapted to resource-poor settings, as it needs refrigeration.
- One positive step is the entry of the Drugs for Neglected Diseases *Initiative* into the field of paediatric HIV drug development, following an R&D needs assessment that showed how HIV infected children are a neglected population.

Generic competition continues to bring down the price of some key medicines.

- The price of the most affordable generic source of heat-stable lopinavir/ritonavir ($402 ppy

Continued above right

Continued from previous page

– offered for all countries) is lower than the most discounted price offered by Abbott ($410 ppy – reserved for least-developed countries and sub-Saharan Africa). The entry of generic manufacturers is having a positive effect on the market, and prices are declining for this crucial second-line drug. However Abbott's product continues to dominate the developing world where the company captured 81% of the market share in 2008.[16] Compulsory licences on lopinavir/ritonavir issued by Thailand in 2007 and Ecuador in 2010 brought the price of the drug down considerably in those countries.

- The price of efavirenz also decreased significantly (to $52 ppy), due to an increase in purchase volumes, and to a new synthesis process which reduces the price of the active pharmaceutical ingredient. Compulsory licences on efavirenz issued by Thailand and Brazil in 2007 brought the price of the drug down considerably in those countries.
- In late 2010, patent applications were rejected in India for atazanavir and lopinavir/ritonavir, both recommended by WHO for second-line AIDS treatment, in rulings that allow generic production to continue and act as an encouragement to other producers to compete for the market and lower the price further. The decisions also serve to highlight India's role as pharmacy of the developing world, and the risks of any further tightening of intellectual property protection through the EU-India or EFTA-India free trade agreements currently under negotiation.
- A divisional patent application was also rejected in Brazil on tenofovir, after opposition from civil society organisations in 2011.

Price remains a barrier for newer medicines, however.

- Rilpivirine, approved this year by US FDA, has the potential for use in long-acting formulations,[14] and its potential low price. At the time of going to press, neither Johnson & Johnson nor the generic companies that had signed licensing agreements with Johnson & Johnson had announced any discounted price for developing countries.
- Prices for salvage therapy are particularly concerning. The prices offered by Johnson & Johnson remain unaffordable for the developing world with darunavir priced at $1,095 ppy and etravirine at $913 ppy. For the first time a price has been announced for LDCs and sub-Saharan Africa for maraviroc, but at $1,584 ppy, this is too high.

Pharmaceutical companies must do more to ensure access to medicines through voluntary measures.

- **Tibotec / Johnson & Johnson** signed licensing agreements with a limited number of generic manufacturers for darunavir (DRV), etravirine (ETV), and rilpivirine, but the terms are too restrictive. First, they exclude all of Latin America, Central Asia and most Caribbean and South-East Asian countries. Second, they do not open competition up enough. The licence for ETV is only with one company and only for distribution in sub-Saharan Africa. The DRV licence includes in addition one Indian company for distribution in India. Licences such as these show the limits of voluntary licences and leave many developing countries with HIV/AIDS burdens without access to affordable versions of these new medicines.
- **Brazil** has announced that it is working on technology transfer agreements with certain manufacturers in order to secure local production for raltegravir and atazanavir. While seeking to secure local production can be an important way to ensure access to medicines, the terms on which such agreements are made and the price discounts achieved are critically important. There may be a risk that this approach does not ensure prices come down as much as through unrestricted generic competition; if so, this would establish a precedent for accessing other newer medicines at higher prices in the future, both in Brazil and beyond. Countries will need to carefully consider the possibility of price increases in the short-term and ensure that there are supporting policies in place to ensure that health budgets can continue to support any such increases.
- **The Medicines Patent Pool,** formally created in July 2010, received its first licence from the US National Institutes of Health in September 2010 for a patent on DRV. Yet the licence itself does not allow for the production of DRV, as further patents are held by Johnson & Johnson. Significantly, the licence was for all developing countries, including those in the middle-income bracket. The pool has received significant political backing from WHO, the G8, and a number of countries who have made it clear that collective action is needed from companies to match the commitments from countries to tackle the HIV epidemic. Four pharmaceutical companies are currently in negotiations with the Pool (Gilead, Roche, ViiV and Sequoia), but MSF is urging all entities that hold patents on HIV drugs to share their patents with the Pool.
- Given the implementation of the TRIPS Agreement in generic-producing countries, governments will need systematically to pursue compulsory licences, as authorised under TRIPS, to enable generic production that will reduce the price of newer AIDS medicines. Countries should be supported in their right to do so and should not face retaliatory measures.