



UNTANGLING THE WEB OF

# ANTIRETROVIRAL PRICE REDUCTIONS

14th Edition July 2011

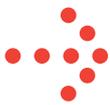


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## **UNTANGLING THE WEB ONLINE!**

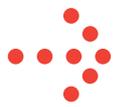
Médecins Sans Frontières' guide to the prices of AIDS medicines is now in its 14th edition – and is also available in an online version. Stay up-to-date with the latest news on ARV prices and availability by checking:

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## **THE MSF CAMPAIGN FOR ACCESS TO ESSENTIAL MEDICINES**

In 1999, on the heels of Médecins Sans Frontières (MSF) being awarded the Nobel Peace Prize – and largely in response to the inequalities surrounding access to AIDS treatment between rich and poor countries – MSF launched the Campaign for Access to Essential Medicines. Its sole purpose has been to push for access to, and the development of life-saving and life-prolonging medicines, diagnostics and vaccines for patients in MSF programmes and beyond.



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# 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.<sup>1</sup>

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.<sup>2</sup> 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.<sup>3</sup>

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.<sup>4</sup> 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



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.<sup>3</sup> 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.<sup>1</sup>

The past ten years have been rich in lessons learnt: how bringing treatment to primary health centres and rural clinics, closer to where people live, 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*.<sup>5</sup>

<sup>1</sup>Defined as reaching 80% of people in need of HIV/AIDS treatment.

<sup>5</sup>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).<sup>4</sup> 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),<sup>5</sup> 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).<sup>6</sup> This call was repeated in the latest guidelines released by WHO in 2010,<sup>7</sup> 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.<sup>8</sup>

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.<sup>10</sup> 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.<sup>10</sup> This is encouraging news, but some countries have been prevented from making the switch because of funding constraints.

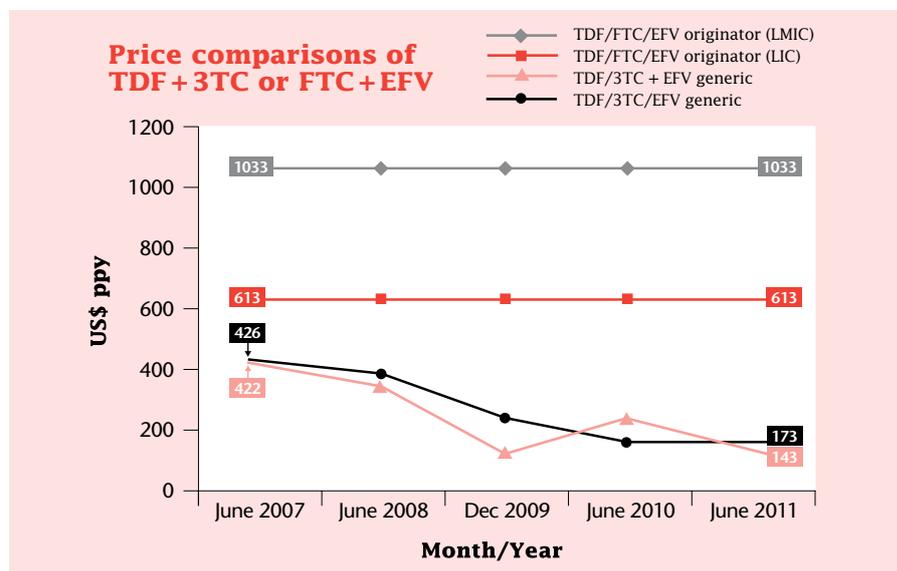
In the price analysis for this edition we found a noteworthy downward trend in the prices of improved (tenofovir-based) first-line combinations, and prices can be expected to fall further as demand increases. In countries where the drugs are not under patent or where patents owners permit generic competition, 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.<sup>11</sup> 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 discounted prices to all lower middle- and upper middle-income countries. Abbott specifically excludes lower middle-income and low-income countries outside of Africa from differential prices for the heat-stable ritonavir 100mg tablet. Tibotec / Johnson & Johnson are also excluding all middle-income countries from differential prices 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.



<sup>11</sup> 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%<sup>11</sup> 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.<sup>13</sup>

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.<sup>7</sup>

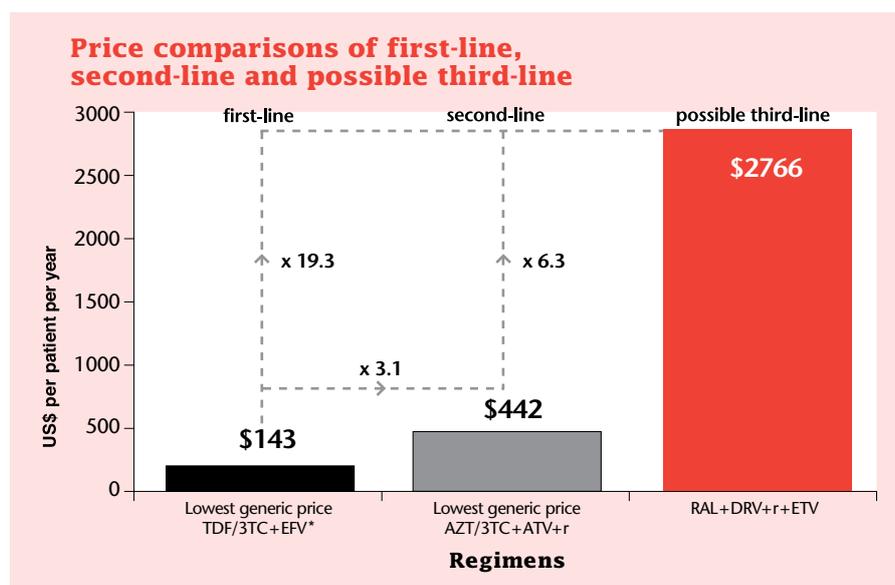
## TREATMENT FAILURE UNDER-DIAGNOSED

The routine, six-monthly, measurement of viral load is a WHO-recommended diagnostic tool for monitoring all HIV positive patients on ART.<sup>6</sup> 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.<sup>19, 21, 46</sup> 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.<sup>100</sup>

## 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.



\*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 than a TDF/3TC + EFV co-pack), its price (\$173) remains higher than the co-pack (\$143), in the absence of competition from further manufacturers.

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### ❖ Ensuring access to treatment options for second-line and beyond continued

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 price discounts to lower middle-income countries altogether.

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.



## 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<sup>14</sup> – and its potential for use in long-acting formulations – an injectable nano-suspension

of rilpivirine has been developed and showed promise for monthly dosing.<sup>14</sup> 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.<sup>15</sup> 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.

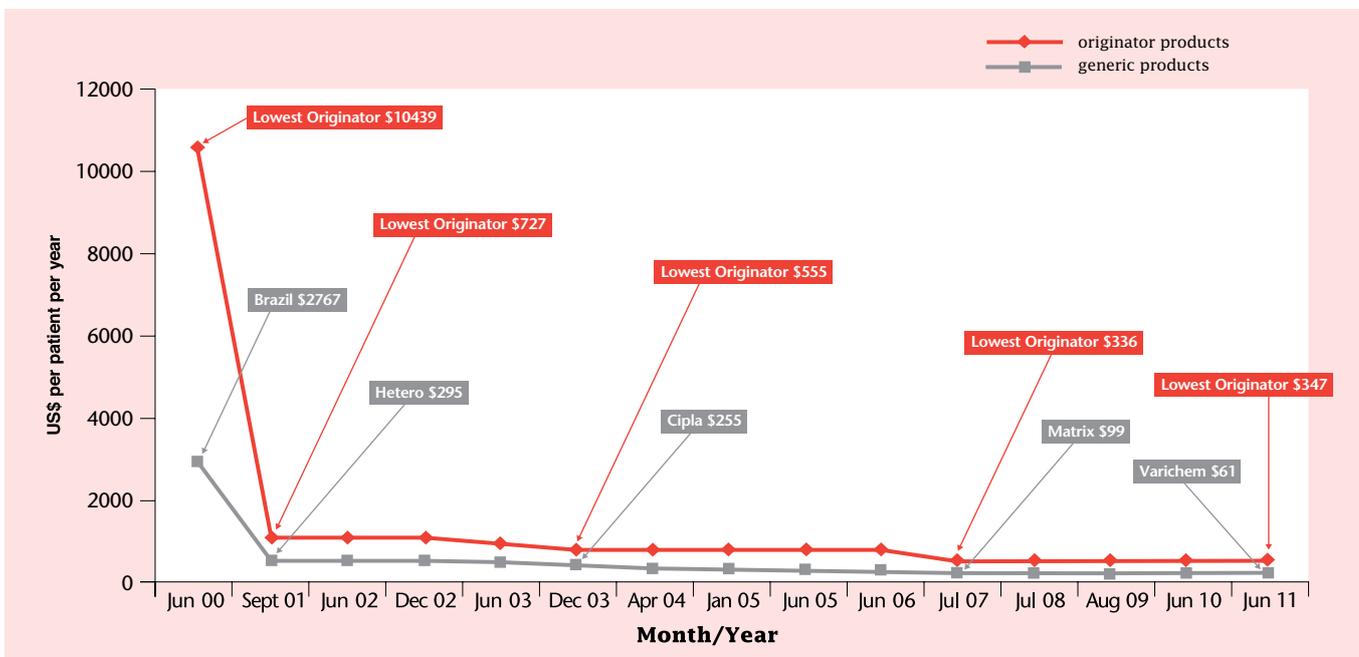
## ENSURING GENERIC PRODUCTION AND REINING IN DRUG COSTS

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.<sup>16</sup>

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.





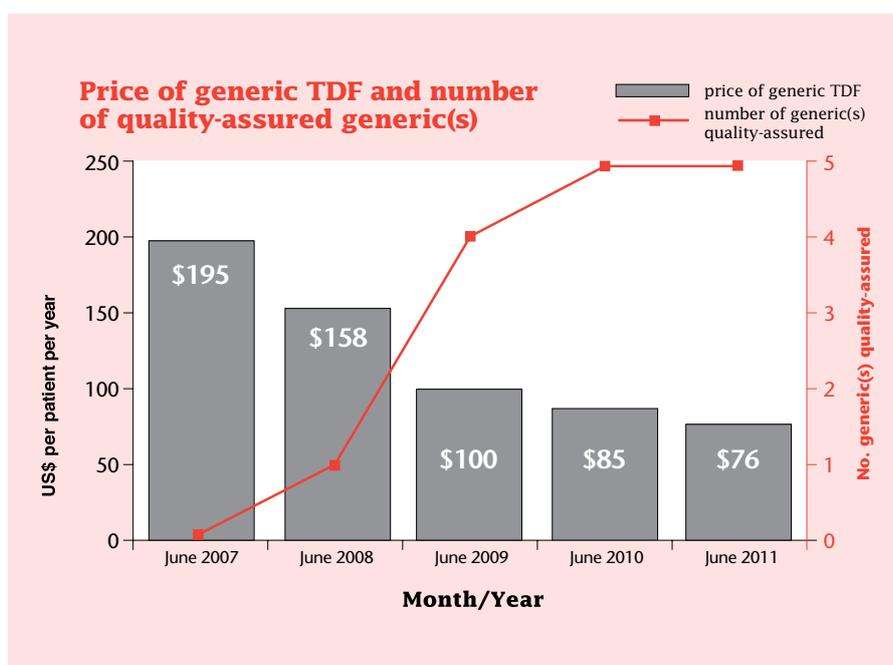
**GRAPH 3: GENERIC COMPETITION AS A CATALYST FOR PRICE REDUCTIONS.**

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

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⚙️ *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.<sup>324</sup>
- 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](http://action.msf.org)

## HIGHLIGHTS FROM THE 14<sup>TH</sup> 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 reduced prices. 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 differential prices 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 discounted prices 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.

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

- Although **Abbott** offers two tiers of differential pricing 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 differential prices for the standalone heat-stable ritonavir 100mg tablet.
- **Tibotec / Johnson & Johnson** also exclude all middle-income countries from differential prices 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

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- 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.<sup>16</sup> 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,<sup>14</sup> 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.



# QUALITY ISSUES

**This report is a pricing guide, and as such does not include detailed information about the quality of the products listed. However, quality is important and price should not be the only factor determining procurement decisions.**

Readers and purchasers wishing to obtain more information about drug quality are therefore encouraged to consult the WHO List of Prequalified Medicinal Products which contains the products that 'meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis medicines' or the US FDA Approved and Tentatively Approved Antiretrovirals List.

## WHO PREQUALIFICATION

More commonly known as WHO Prequalification, the WHO List of Prequalified Medicinal Products was initiated by the WHO and developed in collaboration with other United Nations organisations, principally for procurement by UN agencies. The project evaluates pharmaceutical manufacturers and products according to WHO-recommended standards of quality and compliance with Good Manufacturing Practices.

WHO's Prequalification Programme is a benchmark for the identification of quality essential medicines and has significantly improved access to quality medicines over the past years. A key factor of success has been that financial support to national programmes has been dependent on purchasing medicines respecting clear quality assurance criteria. In this the WHO Prequalification Programme has played an important role, providing guidance to purchasers on the quality of medicines and thereby creating a positive market dynamic where manufacturers strive to reach WHO standards in order to comply with procurement policies.

## US FDA

In May 2004, in support of the US President's Emergency Plan for AIDS Relief (PEPFAR), US FDA announced a new initiative to help ensure that those being served by PEPFAR would receive safe, effective, and quality manufactured antiretroviral drugs.

## DONOR PROCUREMENT POLICIES

The Global Fund to Fight AIDS, Tuberculosis and Malaria has recently changed its quality assurance policy so that Global Fund grant funds may only be used to procure antiretrovirals, anti-tuberculosis and anti-malarial finished products that are either prequalified by the WHO Prequalification Programme, authorised for use by a Stringent Drug Regulatory Authority (SRA), or recommended for use by an Expert Review Panel (ERP).

Unfortunately, the majority of donors today do not have sufficient quality assurance criteria, giving a wrong signal to manufacturers by removing the incentive to comply with WHO norms and standards, and ultimately endangering patients' health in countries where the regulatory system remains weak. Donors and drug purchasers should take heed from the Global Fund's example and make sure that they implement an effective quality assurance policy for medicines bought on behalf of developing countries.

## QUALITY OF DRUGS IN THE DATA PROVIDED IN UNTANGLING THE WEB

Manufacturers who have at least one antiretroviral quality-assured by WHO Prequalification or US FDA were invited to participate in this publication.

But not all the products listed in this report have been quality-assured by WHO Prequalification or US FDA, and only some of them are used by MSF in its own projects. Products included in the List of Prequalified Medicinal Products (as of May 2011), including the ones approved by Health Canada, the European Medicines Agency (EMA) through article 58, or in the US FDA Approved and Tentatively Approved Antiretrovirals List, appear in **bold** in the tables of drug prices.

Please consult the websites for WHO Prequalification<sup>17</sup> and the US FDA Approved and Tentatively Approved Antiretrovirals<sup>18</sup> for the latest list of prequalified products and for information on the status of dossier assessment.

Questionnaires were sent to both originator and generic companies manufacturing antiretrovirals (ARVs), requesting information on prices for developing countries, restrictions that apply to each of the prices quoted (eligibility criteria), and any additional specificity applicable to the quoted prices. The data were collected up to May 2011.

All originator companies marketing ARVs were included in the survey. But the list of generic producers is by no means exhaustive. Only generic companies that have at least one ARV quality-assured by WHO Prequalification or US FDA on the date of requesting price information were included in this publication. Initial questionnaires were sent to companies in early April 2011.

A few generic manufacturers – Huahai, Combino Pharm S.L. and Macleods – were invited to contribute to this publication but have chosen not to provide price information.

### **SOME IMPORTANT PRELIMINARY REMARKS ON THE DATA PRESENTED IN THIS REPORT:**

- The information on prices given in this publication only relates to ARVs. It does not include other costs linked to antiretroviral treatment, such as diagnosis, monitoring or treatment of opportunistic infections. For information on the prices of these products, please refer to 'International Drug Price Indicator Guide' and for paediatric drugs, 'Sources and prices of selected medicines for children'.
- The manufacturers provide the prices listed in this publication. The prices paid by the purchaser might be higher because of add-ons (such as import taxes and distribution mark-ups), or may be lower after negotiations. The document should not be viewed as a manufacturers' price list, and procurement agents are advised to contact manufacturers directly to confirm prices.
- Companies use different trade terms (known as incoterms). These trade terms outline the responsibilities of the manufacturer and purchasers with regard to transport, international freight and insurance costs. Additional information and definitions of incoterms can be found in the 'Glossary and Abbreviations' section at the end of this guide. Prices in the publication have not been adjusted to incorporate the different terms. In 2005, the U.S. General Accountability Office demonstrated that these differences do not undermine their essential comparability.
- Information on patents is only indicative and should be checked with national authorities. It should in no way form the basis of a procurement decision.
- As the information on the WHO Prequalification and the US FDA lists are updated regularly, the lists should be consulted for up-to-date information regarding quality.
- Originator and some generic companies have different eligibility criteria for differential pricing for countries and entities, meaning not all countries and entities can access the price that is mentioned in this guide. The different categories of prices are detailed on the drug profile pages. More detailed information on the different eligibility criteria is provided in Annexes 2-10.
- The Clinton Foundation's Health Access Initiative negotiates prices for ARVs and diagnostic tests with generic companies on behalf of national AIDS programmes included in their consortium. The Clinton Foundation has reached agreements with eight ARV manufacturers to lower the prices of 40 different ARV formulations, both paediatric and adult. The current CHAI price list can be found in Annex 13.

# HOW TO READ THE DRUG PROFILES

## GENERAL INFORMATION

General information on the history of the product and relevant WHO guidance is provided for each of the antiretrovirals (ARVs) included in this publication.

## TABLE ON PRICE INFORMATION – DEVELOPING COUNTRY PRICES AS QUOTED BY COMPANIES

All prices are quoted in United States Dollars (US\$). Currency conversions were made on the day the price information was received using the currency converter site [www.oanda.com](http://www.oanda.com). Prices are rounded up to the third decimal for unit price and to the nearest whole number for yearly price per patient.

The annual cost of treatment per patient year (ppy) has been calculated according to the WHO dosing schedules<sup>6</sup> multiplying the unit price (one tablet, capsule or millilitre) by the number of units required for the daily dose, and by 365. The price of the smallest unit is included in brackets. Where no WHO guidelines exist for a product, the dosage used is the US FDA approved dosage.<sup>20</sup>

For paediatric treatments, prices are calculated for a 10kg child using recommended dosing based on weight bands, as it appears in the WHO treatment guidelines.<sup>6</sup> This is an estimate, as the weight of a child increases during any given year. When it was not possible to calculate the dose for a 10kg child, only the unit price is indicated. For paediatric FDCs, the dosages used for the calculation are those recommended by the Paediatric Antiretroviral Working Group at WHO.<sup>22</sup>

## ACCESS TO PRICE DISCOUNTS – CATEGORIES 1 AND 2

When originator companies apply discounted prices on ARVs, each has different eligibility criteria. This means that a country that is eligible for a price discount from one company may be excluded from the list of eligible countries by another company. In this document, the term ‘first category’ or ‘category 1’ is used to describe those countries that are eligible for the most discounted price offered by a company. The term ‘second category’ or ‘category 2’ is used to describe countries that are not eligible for the lowest prices reserved for category 1 countries, but are nevertheless offered a discount by companies – crucially, this discount is usually considerably smaller than the discount offered to category 1 countries.

To know whether a country is eligible for a discounted price offered by a given company, or to find out in which category a given country is placed by different companies, please refer to the annexes.

## QUALITY

The WHO Prequalification Programme is a service provided by the World Health Organization (WHO) to facilitate access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis. Products quality-assured by WHO Prequalification Programme or US FDA (as of May 2011) are in **bold** in the tables of drug prices.

Readers and purchasers wishing to obtain more information about the quality of ARVs are encouraged to consult the WHO Prequalification Programme website<sup>1</sup> and the US FDA website<sup>2</sup> for approved and tentatively approved ARVs, as these lists are updated regularly.

## CLINTON PRICES

The Clinton Health Access Initiative (CHAI) negotiates with several manufacturers for reduced prices for almost 40 different ARV formulations for countries in their pooled procurement consortium. Manufacturers who have a product included in the most recent price announcement are indicated by a (CF) in the header of the table. Further details of the specifics of the product can be found in Annex 13.

## PRICE CHANGES OVER TIME – CHART ON THE EVOLUTION OF THE LOWEST PRICE QUOTED FOR DEVELOPING COUNTRIES

This chart shows the price evolution over time, for both originator and generic products, as quoted to MSF for the purpose of this document since 2001.

If a generic product quality-assured by WHO Prequalification or US FDA is available, the graph shows the lowest-priced quality-assured generic product. If no generic product is quality-assured by WHO Prequalification or US FDA, the lowest-priced product is considered in the graph, regardless of quality status.

## SPOTLIGHT ON ACCESS ISSUES – A LOOK AT PATENTS AND PAEDIATRICS

The most salient issues related to access to each product are summarised here. The focus is on the availability of products, their affordability and their adaptability for the developing world.

A special comment has been included when appropriate with regard to patents and paediatrics.

<sup>1</sup><http://apps.who.int/prequal/>

<sup>2</sup><http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm>

# ABACAVIR (ABC)

## GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- WHO guidelines: Indicated for first- and second-line for adults, adolescents and children.<sup>6,22</sup>
- Originator company and product brand name: GlaxoSmithKline (GSK), Ziagen. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): December 1998.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- World sales of originator product: 2010: Sales not reported. 2009: US\$ 160 million; 2008: \$175 million; 2007: \$215 million; 2006: \$230 million; 2005: \$268 million; 2004: \$290 million.<sup>25, 26, 27, 28, 29, 30</sup>
- Patents: The basic patents on ABC were applied for by GSK in 1989<sup>31</sup> and 1990,<sup>31</sup> and these expired in 2009 and 2010, respectively. GSK subsequently applied for additional patents related to new intermediates in 1995,<sup>32</sup> to the hemisulfate salt of ABC in 1998<sup>33</sup> and to compositions of ABC particularly relevant for paediatric use in 1999, which<sup>34</sup> are due to expire in 2015, 2018 and 2019, respectively.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

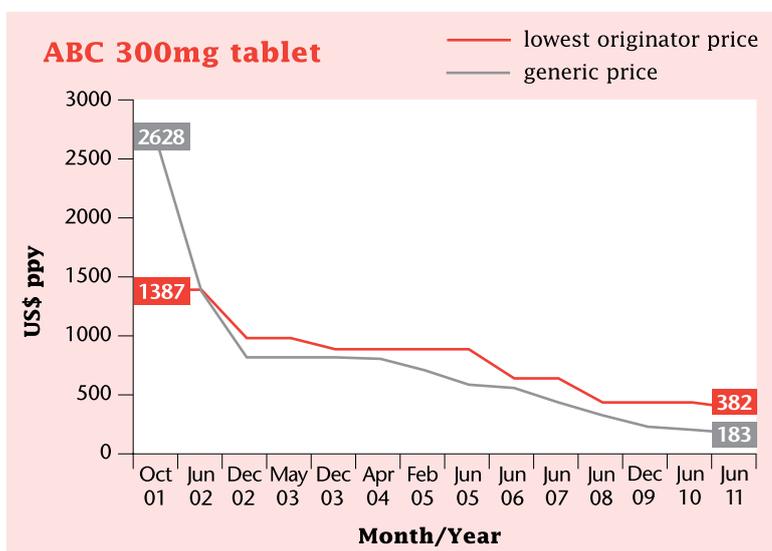
	Daily dose	ViiV	Aspen	Aurobindo (CF)	Cipla (CF)	Hetero	Matrix (CF)	Ranbaxy	Strides
Who can access this price?		See annex 2							
ABC 20mg/ml oral solution	10 ml	<b>347 (0.095/ml)</b>	153 (0.042/ml)	<b>212 (0.058/ml)</b>	<b>139 (0.038/ml)</b>				
ABC 60mg tablet	4			<b>146 (0.100)</b>	<b>158 (0.108)</b>		<b>134 (0.092)</b>		
ABC 300mg tablet	2	<b>382 (0.523)</b>		<b>195 (0.267)</b>	<b>231 (0.317)</b>	<b>231 (0.317)</b>	<b>183 (0.250)</b>	<b>261 (0.358)</b>	<b>292 (0.400)</b>

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest price quoted for eligible developing countries since 2001:

As of May 2011, six generic sources of ABC 300mg tablet were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

Since 2001, the originator price has decreased by 72%, while generic prices have dropped by 93%.



Continued overleaf

## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. For second-line treatment, protease inhibitors such as ritonavir-boosted atazanavir (ATV/r) or lopinavir (LPV/r), and simplified NRTI options are recommended. Abacavir (ABC) (along with didanosine (ddI)) is therefore no longer recommended as one of the NRTI backbones in second-line therapy.<sup>7</sup>

Price remains an issue. Even though the generic price of ABC has fallen by 93% since 2001, the current lowest price is more than twice the lowest price of tenofovir (TDF) or zidovudine (AZT).

In addition, in 2011, ViiV clarified their pricing structure (see annex 2), confirming that their differential prices 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 those prices, and will have to negotiate prices on a case-by-case basis. With some developed countries paying over \$3,500 ppy, the price is prohibitive for many developing countries that need to access the product.<sup>35</sup>

In February 2011, Shionogi-ViiV Healthcare announced the start of a phase III trial for a new fixed-dose combination including ABC, lamivudine (3TC)<sup>36</sup> and a new integrase inhibitor S/GSK1349572 (an investigational drug known as dolutegravir, now in phase III clinical development).<sup>37</sup>

### Patents

The price of ABC decreased significantly with the arrival of generic competition. GSK could not apply for the basic patents on ABC in countries with generic production capacity such as India, which did not grant patents on pharmaceuticals at the time.

However, patents have been granted in China.<sup>38</sup>

In addition, GSK applied for patents on the hemisulfate salt of ABC in India but withdrew this application in October 2007 after it was opposed by civil society groups in a pre-grant opposition procedure.<sup>39</sup>

GSK also applied for a patent on compositions of ABC particularly relevant for paediatric use, which was granted in December 2007.<sup>40</sup>

This patent raises concerns over the continued generic availability of the ABC paediatric formulation, which is an important option for young children with HIV/TB co-infection.

### Paediatrics

ABC is approved for use in children. In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends ABC as one of the possible NRTIs to be given with 3TC and either an NNRTI or a PI in the first-line. WHO guidelines recommend a preferential order of NRTIs to be used in first-line regimens, with AZT preferred over ABC, and ABC preferred over d4T.<sup>22</sup>

ABC can also be part of second-line regimens, depending on what has been used as a first-line.<sup>22</sup>

ABC will continue to be an important drug for HIV/TB co-infected young children, not least because children have limited treatment options – there are interactions between TB drugs and nevirapine (NVP), and the dosage data on efavirenz (EFV) for children under three is lacking.

However, a recent survey regarding paediatric second-line carried out by the TREAT Asia Paediatric HIV Observational Database (TApHOD) found that ABC was more difficult to access in Asia and that its relatively high cost could act as a deterrent to wider use.<sup>41</sup> This applies particularly in countries where ABC is patented, where the generic ABC 60mg tablet is not available. In the public sector in Malaysia, ViiV's ABC solution costs more than \$1200 ppy.<sup>42</sup>

Paediatric ABC comes in a liquid formulation. In addition, as of April 2011, three generic sources of ABC 60mg paediatric tablet are quality-assured by either US FDA or WHO prequalification.

Generic manufacturers have also been developing both double and triple fixed-dose combinations containing ABC. As of May 2011, two sources of paediatric double FDC and one triple FDCs containing ABC were quality-assured by either US FDA or WHO prequalification. All are produced by generic companies.

Once-daily dosing of ABC is only recommended for patients over 12 years of age; more studies are needed to confirm the safety of daily dosing of ABC in children.<sup>43</sup>

# ATAZANAVIR (ATV)

## GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- Patents: The basic patent was filed in April 1997 by Novartis and is expected to expire in April 2017.<sup>50</sup> Bristol-Myers Squibb is manufacturing ATV under licence from Novartis. BMS also applied for patents on the crystalline bisulfate salt of ATV in December 1998<sup>51</sup> and on a process for preparing the bisulfate salt and novel forms in 2005.<sup>52</sup>
- WHO guidelines: Boosted ATV is indicated for second-line for adults and adolescents.<sup>6</sup>
- World sales of originator product: 2010: US\$ 1.5 billion; 2009: \$1.4 billion; 2008: \$1.3 billion; 2007: \$1.1 billion; 2006: \$931 million; 2005: \$696 million; 2004: \$369 million; 2003: \$81 million.<sup>44, 45, 116, 47, 48, 49</sup>
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Reyataz.
- First approval by U.S. Food and Drug Administration (FDA): June 2003.<sup>23</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one capsule. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

	Daily dose	BMS		Emcure (CF)	Matrix (CF)
		Category 1 countries	Category 2 countries		
Who can access this price?		See annex 2 & annex 7		See annex 2	
ATV 100mg capsule	3*			<b>(0.267)</b>	
ATV 150mg capsule	2*	<b>412 (0.565)</b>	<b>547 (0.749)</b>	<b>268 (0.367)</b>	<b>426 (0.583)</b>
ATV 200mg capsule	-	(0.677)	(0.942)	<b>(0.483)</b>	
ATV 300mg capsule	1*			<b>268 (0.733)</b>	<b>250 (0.686)</b>

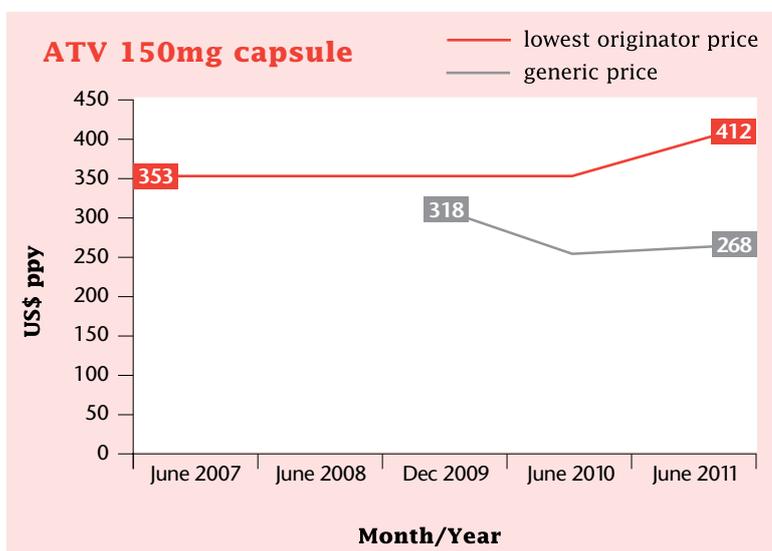
\*The dose of ATV must be boosted with RTV 100mg once a day in treatment experienced patients.

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest price quoted for eligible developing countries since 2007:

As of May 2011, two generic sources of ATV 150mg capsule were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

Last year, for the first time since 2007, the originator price increased by 17%, while generic prices have dropped by 16% since 2009.



Continued overleaf

## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors (PI), to be taken in combination with two NRTIs. They are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r).<sup>7</sup> With its once-a-day dosing ATV is the more patient-friendly PI of the two.

ATV, like all PIs (with the exception of nelfinavir (NFV), requires boosting with RTV. Abbott's heat-stable ritonavir received marketing approval in the U.S. and Europe in early 2010. Registering this new formulation in developing countries will be crucial in order to allow the use of other PIs than lopinavir. A generic heat-stable RTV is now available and was WHO prequalified in late 2010.

As ATV is one of the two PIs recommended by WHO, there is an urgent need for generic manufacturers to supply a heat-stable ATV/r fixed-dose combination. Currently this fixed-dose combination is not produced by the originator companies.

In some African countries including Ethiopia, Ghana, Kenya, Nigeria, Tanzania and Uganda, Bristol-Myers Squibb (BMS) discontinued all commercial activities by the end of 2009, including deregistration of all BMS products.<sup>53</sup>

### Patents

In most developing countries with generic pharmaceutical production capacity, including Brazil, China and India, Novartis and BMS filed patent applications related to the ATV compound,<sup>54</sup> bisulphate salt,<sup>55</sup> which is the best route to making ATV<sup>56</sup> and its combination with other ARVs.<sup>57, 58, 59, 60</sup> Most patents have been granted in Brazil and China.

In India, where ATV is already under generic production, patent applications are still under examination. Civil society organisations filed a pre-grant opposition<sup>61</sup> to Novartis's basic patent application<sup>62</sup> on the grounds of lack of novelty.<sup>63</sup> The patent application has since been abandoned,<sup>64</sup> but several divisional patent applications<sup>65, 66</sup> have been filed by Novartis. In

addition, a single patent application filed by BMS in 2006 contained claims that covered the most efficient route of manufacturing ATV and its bisulphate salt.<sup>67</sup> This application was opposed by generic companies and the patent office recently rejected the application.<sup>68</sup> However, BMS had already filed a divisional patent application<sup>69</sup> which is pending before the Indian patent office. These divisional and other patent applications on ATV and its use in combination with other ARVs<sup>70, 71, 72, 73</sup> warrant additional pre-grant oppositions.<sup>74</sup>

In addition, Abbott has filed patent applications on RTV in India and other developing countries which, if granted, will block the development of and access to generic ATV/r fixed-dose combinations.

In February 2006, BMS granted technology transfer and voluntary licences to two generic manufacturers (Emcure and Aspen) to manufacture and sell ATV. In February 2008, Emcure received US FDA tentative approval for the 100mg, 150mg and 200mg ATV capsules. Under the terms of the licences, however, sales of these products are royalty-free but are restricted to sub-Saharan Africa. BMS has a separate agreement with Emcure that covers India.<sup>75</sup>

Licensing agreements in India should not be necessary if patent oppositions are successful. If patents are granted, India and other countries could issue compulsory licences to enable unrestricted competition from generic manufacturers, in order to bring prices down, increase access and facilitate the development of an ATV/r fixed-dose combination.

BMS's differential pricing structure is limited to sub-Saharan Africa and low-income countries. This structure leaves middle-income countries such as Brazil paying more than \$1,000 per patient per year, a prohibitive price for many of these countries.<sup>76</sup>

In Brazil, BMS's monopoly led to shortages of ATV in 2005<sup>77</sup> and 2011,<sup>78</sup> and several patients had to change

treatment regimens. Civil society groups then urged the government to issue a compulsory licence (CL) arguing Brazilian law justified the measure.<sup>79</sup> After the second shortage however, the government announced the creation of a public-private partnership for the local production of ATV,<sup>80</sup> preferring to negotiate with BMS rather than issue a CL to stimulate the local production of more affordable generic versions. The reasons for this choice remain unclear, and civil society groups continue to demand transparency on this agreement, particularly since it involves a publicly-owned laboratory.<sup>81</sup> To date, no information concerning price reductions or sales restrictions for this product has been made available.

In 2011, a year's treatment using the 300mg tablet in Brazil cost \$1,022. By April 2011, around 40,450 patients in Brazil were taking ATV as part of their treatment regimen.<sup>82</sup>

### Paediatrics

In March 2008, ATV was approved for use in children between six and 18 years of age.<sup>23</sup> No formulation exists for children.

In addition, ATV must be given with a RTV booster, but the RTV solution currently available has a bitter aftertaste and contains 43% alcohol, and is thus not adapted for children, limiting the use of ATV in this population.

In 2008, WHO recommended early treatment for all HIV-positive children, and children who have been exposed to nevirapine (NVP) either through their mother or through a single dose in a prevention of mother-to-child transmission programme. WHO recommends these children should be started on a PI-based regimen.<sup>22</sup> Today, the only option for these children is the LPV/r formulation.

To simplify treatment for all children, there is an urgent need for studies on ATV to be completed in infants and children under six, and child-adapted formulations of ATV and ATV/r to be made available.

# DARUNAVIR (DRV)

## GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- WHO guidelines: Boosted DRV is listed as a potential third-line drug.<sup>6</sup>
- Indication: For treatment-experienced patients, such as those with HIV-1 strains resistant to more than one protease inhibitor (adults). It is also indicated in developed countries for treatment-naïve adult patients.<sup>83</sup>
- Originator company and product brand name: Tibotec (a subsidiary of Johnson & Johnson), Prezista.
- First approval by U.S. Food and Drug Administration (FDA): June 2006.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Not included in the 17th edition.<sup>24</sup>
- World sales of originator product: More than US\$ 1 billion.<sup>84</sup>
- Patents: The basic patent was applied for by Searle and Monsanto in August 1993,<sup>85</sup> and is due to expire in 2013. Subsequently, NIH and the University of Illinois applied for patents more specifically related to darunavir in 1999<sup>86</sup> and licenced them to Tibotec for development.<sup>87</sup> Tibotec later applied for patents related to improved forms and combinations of darunavir.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet.

	Daily dose	Tibotec
Who can access this price?		See annex 2
DRV 300mg tablet	4*	1095 (0.750)

\*The dose of DRV must be boosted with RTV 100mg twice a day.

Continued overleaf ❖

## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations which for the first time call for the need of third-line therapy. Many studies are ongoing – drugs likely to have anti-HIV activity in third-line regimens are boosted darunavir (DRV), etravirine (ETV), and raltegravir (RAL).<sup>7</sup>

DRV, like all protease inhibitors (PIs) (with the exception of nelfinavir (NFV)), requires boosting with ritonavir (RTV). Abbott's heat-stable ritonavir received marketing approval in the U.S. and Europe in early 2010. Registering this new formulation in developing countries will be crucial in order to allow the use of other PIs than lopinavir. A generic heat-stable RTV is now available and was WHO prequalified in late 2010.

Patient numbers in Africa for DRV are still small.

Tibotec (a subsidiary of Johnson & Johnson) signed a royalty-free, non-exclusive licence agreement with Aspen of South Africa in April 2007. This grants Aspen the right to register, package and distribute DRV in sub-Saharan Africa. In December 2008, Tibotec announced the signing of a similar agreement with Emcure to distribute DRV in India.<sup>88</sup> In 2011, Tibotec completed a second supply with Aspen covering the 300mg tablet but also the 600mg tablet. Aspen will distribute the medicine at \$1,095 per patient per year, and plans to replace the DVR 300mg tablet with the 600mg tablet, once it has been approved in most sub-Saharan Africa countries. Despite the VL, the price remains unaffordable for the developing world. At the time of writing, the Aspen/Tibotec product is registered in at least eighteen countries with applications in process in four others. The price per patient per year will remain the same for both presentations.

These agreements exclude other low- and middle-income countries, for which the price paid in wealthy countries, at over \$13,100 per patient per year, is prohibitive.<sup>89</sup>

There is a need for generic manufacturers to supply a heat-stable DRV/r fixed-dose combination, which is currently not produced by the originator companies.

### Patents

The basic patents related to DRV<sup>90</sup> could not be applied for in India as the country did not grant patents on pharmaceuticals before 1995. Tibotec has nevertheless applied for several patents in India related to the pseudo-polymorphic form,<sup>91</sup> the method for preparation of key intermediates<sup>92</sup> of DRV and combinations of DRV with RTV<sup>93</sup> and with both TDF and RTV.<sup>94</sup> Some of these applications have been opposed by generic manufacturers.

The Indian patent office recently rejected several applications related to pseudo-polymorph,<sup>95</sup> the method for preparation of key intermediates and the combination of DRV with RTV.<sup>96</sup> The patent application on the combination of DRV with TDF was withdrawn after opposition.<sup>97</sup> The patent threat to the combination on DRV with RTV continues as Tibotec filed a divisional application<sup>98</sup> (still-pending) at the Indian patent office, along with appeals to the rejections.

In addition, Abbott has filed patent applications on RTV in India and other developing countries which, if granted, will block the development of and access to generic DRV/r fixed-dose combinations.

In China, Tibotec<sup>38</sup> was granted patents related to racemic and pseudo-polymorphic forms of DRV, methods for preparing intermediate compounds of DRV and use of DRV in combination with other ARVs.<sup>38</sup>

Similarly, more than 10 patent applications have been filed in Brazil, such as those related to the combination of DRV with TDF and RTV, as well as those related to the preparation of key intermediates and the pseudo-polymorphic form. In Brazil, DRV was included in the government's guidelines in 2008, but

at \$6,037 per patient per year (boosted with ritonavir), it is very expensive.

In September 2010, the U.S. National Institutes of Health (NIH) licensed a patent on darunavir to the Medicines Patent Pool,<sup>263</sup> a mechanism designed to boost access to more affordable AIDS drugs in the developing world, in a move that demonstrates political backing for the Medicines Patent Pool to benefit all developing countries. The NIH patent will not free the way for generic versions of darunavir, however, because additional patents are held by Tibotec.

### Paediatrics

In December 2008, DRV was approved for use in children between six and 18 years of age.<sup>23</sup> To simplify treatment for all children, there is an urgent need for studies on DRV to be completed in infants and children under six.

A paediatric 75mg tablet is available, but Tibotec has not provided price information for this product. There is no generic paediatric product yet available. The Tibotec product is however available on a compassionate use basis (free of charge) for sub-Saharan Africa and least-developed countries, until a pre-approval access programme is established with a local partner. The tablet is only suitable for children with the ability to swallow.

An added complexity is that DRV must be given with a RTV booster, but the RTV solution currently available has a bitter aftertaste and contains 43% alcohol, and is thus not adapted for children, limiting the use of DRV in this population.

There is therefore a need for child-adapted formulations of DRV/r to be made more widely available. The Paediatric Antiretroviral Working Group of WHO considers the development of a fixed-dose combination containing darunavir and ritonavir to be a high priority, though it is still unclear what the ratio of the co-formulation will be.<sup>22</sup>

# DIDANOSINE (ddl)

## GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- WHO guidelines: Indicated for second-line for children.<sup>22</sup>
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Videx/Videx EC.
- First approval by U.S. Food and Drug Administration (FDA): October 1991 for chewable tablets; October 2000 for enteric-coated capsules.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- World sales of originator product: 2005: US\$ 174 million; 2004: \$274 million; 2003: \$354 million. After 2005, there are no sales figures listed in the company's annual report.<sup>115</sup>
- Patents: The basic patent on ddl filed in 1985 by the National Institutes of Health (NIH), a U.S. government research institute, has expired, but BMS holds patents on improved formulations in some countries, which run until 2012 and 2018.<sup>101</sup>

## PRICE INFORMATION

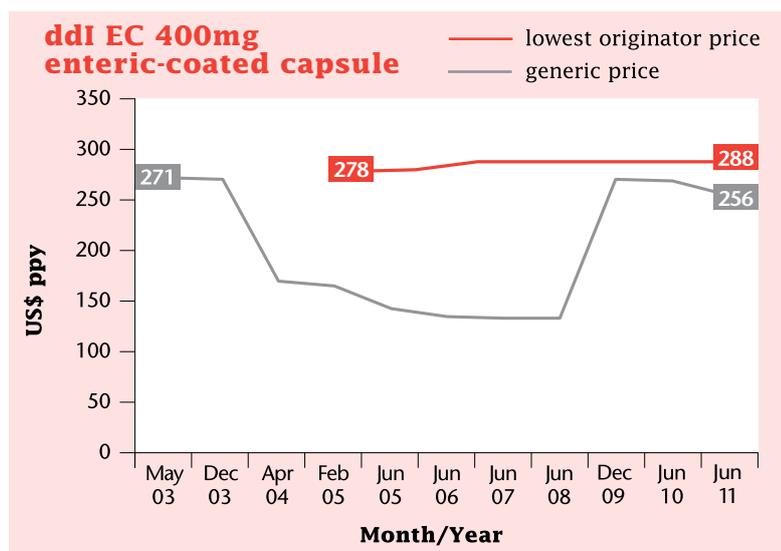
### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet/capsule/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

	Daily dose	BMS		Aurobindo	Cipla	Matrix	Ranbaxy
		Category 1 countries	Category 2 countries				
Who can access this price?		See annex 2 & annex 7		See annex 2			
ddl 2g powder for reconstitution (final concentration 10mg/ml)	12 ml	<b>276 (12.590/2g)</b>	No discounted price				
ddl 25mg tablet	6	<b>256 (0.117)</b>	No discounted price		138 (0.063)		252 (0.115)
ddl 50mg tablet	-	<b>(0.159)</b>	No discounted price		(0.079)		(0.125)
ddl 100mg tablet	-	<b>(0.213)</b>	No discounted price	<b>(0.133)</b>	(0.129)		(0.166)
ddl 125mg enteric-coated capsule	1			<b>110 (0.300)</b>		<b>119 (0.325)</b>	
ddl 150mg tablet	-			<b>(0.225)</b>	(0.167)		
ddl 200mg tablet	-			<b>(0.267)</b>	(0.257)		
ddl 200mg enteric-coated capsule	-			<b>(0.383)</b>		<b>(0.489)</b>	
ddl 250mg enteric-coated capsule	1	<b>223 (0.612)</b>	<b>316 (0.866)</b>	<b>170 (0.467)</b>	103 (0.283)	<b>172 (0.471)</b>	134 (0.367)
ddl 400mg enteric-coated capsule	1	<b>288 (0.789)</b>	<b>408 (1.118)</b>	<b>256 (0.700)</b>	132 (0.363)	<b>268 (0.733)</b>	183 (0.500)

Continued overleaf

Didanosine (ddl) continued



**Evolution of the lowest price quoted for developing countries since 2003:**

As of May 2011, three generic sources of ddl 400mg enteric-coated capsule were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

The first generic source of ddl 400mg enteric-coated capsule was quality-assured by WHO prequalification in June 2008 – the generic price in the graph above corresponds to the lowest generic price until that date, and to the lowest quality-assured generic price from that date on which explains the price increase.

**SPOTLIGHT ON ACCESS ISSUES**

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. For second-line treatment, protease inhibitors such as ritonavir-boosted atazanavir (ATV/r) or lopinavir (LPV/r), and simplified NRTI options are recommended. Didanosine (ddl) (along with abacavir (ABC)) is therefore no longer recommended as one of the NRTI backbones in second-line therapy.<sup>7</sup>

Bristol-Myers Squibb (BMS)'s differential pricing structure limits the prices quoted in this publication to sub-Saharan Africa and low-income countries only. Some wealthy countries pay more than \$4,100 per patient per year for ddl 400mg enteric-coated (EC) capsules, a price which is prohibitive for many developing countries.<sup>102</sup>

The enteric-coated capsules are better suited as they can be taken once daily and, unlike the tablets, do not contain a buffer. The buffer has been associated with stomach upsets and a bitter and chalky taste. In 2006, BMS discontinued the sale of the chewable/dispersible buffered tablets in the U.S. In December 2009, the company also discontinued the sale and manufacturing of ddl 200mg tablet globally due to low demand for the product.

In some African countries including Ethiopia, Ghana, Kenya, Nigeria, Tanzania and Uganda, BMS discontinued all commercial activities by the end of 2009, including

deregistration of all BMS products. BMS also discontinued the marketing of didanosine products in South Africa in December 2010.<sup>106</sup>

**Patents**

No application claiming a patent on enteric-coated capsules has been published in India, allowing a generic version to be launched. However, where the patent has been granted in other developing countries, as in Brazil, China, and in ARIPO and OAPI countries, the importation of the more affordable version from India is blocked.

In Brazil, the active ingredient is in the public domain, which has allowed the government to produce locally the generic version as a powder for oral solution.<sup>107</sup> However, the enteric-coated capsule remains under patent protection.

**Paediatrics**

In October 1991, ddl was approved for use in children between two weeks and 18 years old.<sup>108</sup>

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends ddl be given as part of second-line regimens, depending on what has been used as a first-line.<sup>22</sup>

Paediatric formulations are available. For younger children, however, the only options are buffered tablets that come with a high pill burden, or the ddl powder for reconstitution, which requires multiple dilutions, first with

water and then with an antacid, to obtain the final concentration. Once reconstituted, the solution must be refrigerated and discarded after 30 days.

For older children who can swallow, the best-adapted option is the ddl EC 125mg capsule, but BMS offers no differential price for this product.

In 2007, BMS announced its intention to restructure the company, with plans to reduce the number of brands in the company's mature products portfolio by 60% and reduce the company's manufacturing facilities by more than 50% by 2011.<sup>109</sup> The BMS manufacturing plant in Meymac, France, was closed in June 2010. Fearing disruption in stocks for the developing world – and particularly for up to 7,000 paediatric patients in UNITAID-supported programmes<sup>104</sup> – due to lack of alternative quality-assured generic sources of ddl, civil society organisations<sup>109</sup> demanded that BMS address the foreseen shortage of didanosine 25mg and 50mg tablets ensuing from the plant closure.<sup>104</sup> The WHO also issued a memo warning developing countries of the impending shortage and recommended strategies to avoid treatment disruption including changing regimen.<sup>105</sup> BMS responded by fast-tracking the application for approval of the new plant with WHO prequalification programme by the end of 2010.

There is an urgent need for generic paediatric ddl 25mg tablets to be quality-assured by WHO prequalification.

# EFAVIRENZ (EFV)

## GENERAL INFORMATION

- Therapeutic class: Non-nucleoside reverse transcriptase inhibitor (NNRTI).
- WHO guidelines: Indicated for first- and second-line for adults, adolescents and children.<sup>110,22</sup>
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Sustiva; or Merck, Stocrin.
- First approval by U.S. Food and Drug Administration (FDA): September 1998.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- World sales of originator product: 2010: US\$ 1.4 billion; 2009: \$1.2 billion; 2008: \$1.1 billion; 2007: \$956 million; 2006: \$791 million; 2005: \$680 million; 2004: \$621 million; and 2003: \$544 million.<sup>111, 112, 113, 114, 115, 116</sup>
- Patents: The basic patent on EFV was filed in 1993 by Merck, and is due to expire in 2013.<sup>117</sup> Subsequently, Merck filed for patent applications related to crystallized forms, due to expire in 2018.<sup>118</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet/capsule/suspension dose or oral solution. Products included in the WHO List of Prequalified Medicinal Products (as of May 2011) are in **bold**.

	Daily dose	Merck	Aspen	Aurobindo (CF)	Cipla	Emcure	Hetero	Matrix (CF)	Micro Labs	Ranbaxy	Strides (CF)
Who can access this price?		See annex 2 & annex 10*	See annex 2								
EFV 30mg/ml oral solution	-	<b>(0.094/ml)</b>									
EFV 50mg capsule	-			<b>(0.083)</b>					(0.047)		
EFV 50mg tablet	-	<b>(0.120)</b>						<b>(0.050)</b>			
EFV 100mg capsule	-								(0.042)		
EFV 100mg tablet								<b>(0.117)</b>		(0.150)	
EFV 200mg capsule	3			<b>116 (0.106)</b>	<b>134 (0.122)</b>		152 (0.139)		80 (0.073)	<b>97 (0.089)</b>	
EFV 200mg tablet	3	<b>394 (0.360)</b>						<b>183 (0.167)</b>			<b>113 (0.103)</b>
EFV 600mg tablet	1	<b>237 (0.650)</b>	62 (0.170)	<b>73 (0.200)</b>	<b>79 (0.217)</b>	<b>61 (0.167)</b>	<b>67 (0.183)</b>	<b>55 (0.150)</b>	58 (0.158)	<b>72 (0.197)</b>	<b>52 (0.143)</b>

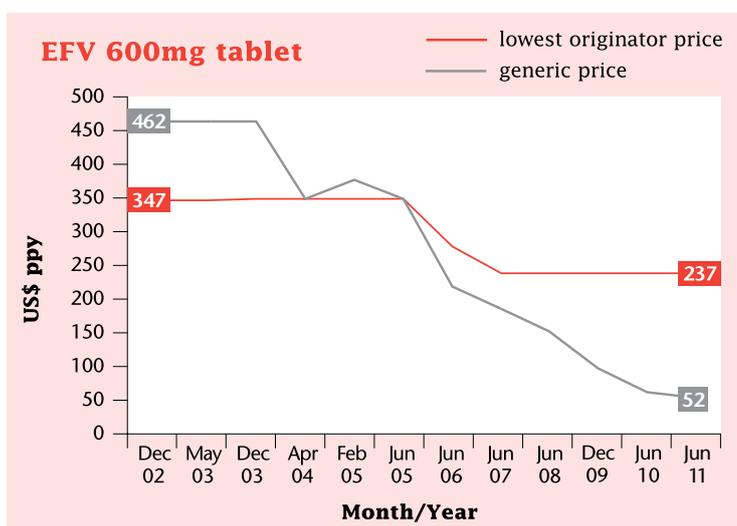
\*For the first time this year, Merck decided not to give discounted prices to Category 2 countries. See 'Spotlight on access issues' below.

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest price quoted for developing countries since 2002:

As of May 2011, seven generic sources of EFV 600mg tablet were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

Since 2002, the originator price has decreased by 32%, while generic prices have dropped by 89%.



Continued overleaf

## SPOTLIGHT ON ACCESS ISSUES

Efavirenz (EFV) is a key drug for first-line treatment, as it is very potent, with once-daily dosing, and is well-tolerated.

In its new 2010 guidelines, WHO recommends the use of EFV – in combination with two NRTIs, one of which should be zidovudine (AZT) or tenofovir (TDF) – as a preferred first-line antiretroviral treatment.<sup>7</sup>

EFV is also recommended as the preferred NNRTI for patients starting ART while on tuberculosis treatment. Rifampicin, one of the main drugs used to treat TB, interacts with nevirapine (NVP), resulting in lower blood levels of NVP. EFV, however, does not have the same degree of interaction, and can be used as an alternative.

Merck has phased out the 200mg and 50mg capsule formulations, which have been replaced by tablets.

In 2011, Merck ceased offering discounted prices to all lower middle- and upper middle-income countries according to the World Bank Classification (see annex 6 for a list of these countries). The company proposes instead to negotiate discounted prices on a case-by case basis, based on country income and disease burden.

This is concerning for the affordability of products in middle-income countries, especially given that Merck's previous pricing strategy (published in previous editions of *Untangling the Web*) was to offer middle-income countries the EFV 600mg tablet at prices more than ten times more expensive than the generic version.

### Patents

Merck does not hold a product patent for EFV in India. Generic competition from a number of Indian manufacturers has thus brought the price down significantly. However, a patent for the process of preparing form 1 of crystalline EFV was granted in June 2005.<sup>119</sup> This process patent appears to protect a key process

for manufacturing EFV. This patent has therefore been opposed by Indian civil society organisations using the post-grant opposition procedures enshrined in India's patent law.<sup>120</sup>

In addition, Gilead<sup>121</sup> and BMS filed patent applications related to combinations of EFV with other ARVs. The patent office has already rejected Gilead's application,<sup>122</sup> as combinations of known molecules are not patentable under India's patent law. BMS's efforts to receive a patent for the once-a-day pill EFV/FTC/TDF<sup>123</sup> could impact on access to improved first-line ARV treatment in the developing world and therefore warrants pre-grant patent opposition, particularly in India.

EFV remains expensive in countries where Merck holds patents that block the production and sale of generics. In countries where EFV is patented, governments and civil society groups have taken various measures to ensure generic competition and lower prices, including:

- In November 2006, Thailand issued a compulsory licence to import generic versions of EFV from India. As a result, the Thai government is now purchasing EFV at \$106 ppy, considerably lower than the previous price of \$511 ppy.<sup>124,125</sup>
- In May 2007, Brazil, after numerous unsuccessful negotiations with Merck, issued a compulsory licence to import more affordable generic versions of EFV from India. At the time, the price of EFV in Brazil was \$580 ppy and had not changed since 2003. After the compulsory licence, Brazil began to import a generic version prequalified by WHO for \$190 ppy. In February 2009, the public manufacturer Farmanguinhos (Fiocruz) launched the national generic version for use in the Brazilian health system.<sup>126</sup>
- In South Africa, Merck's refusal to allow sufficient generic competition contributed significantly to the high price of the drug. This led the AIDS

Law Project, acting on behalf of the Treatment Action Campaign, to file a complaint before the Competition Commission in November 2007. As a result, Merck recently agreed to license its product to other producers, opening the opportunity for generic competition in South Africa, where six suppliers now market EFV or EFV-containing combination products.<sup>127</sup>

### Paediatrics

In 2010, WHO issued updated guidelines for antiretroviral use in paediatric HIV infection. These guidelines recommend that children under three be given two NRTIs plus nevirapine (to be replaced with lopinavir/ritonavir in case of peripartum nevirapin exposure); for children > 3 years the recommended regime is two NRTIs plus efavirenz (or lopinavir/ritonavir).

Although EFV was approved by US FDA for use in adults in 1998, there is still no established dosing of the medicine for children less than three years of age. There is an urgent need to establish the dosing of EFV for this age group, which is critical for children with HIV/TB co-infection.

In the absence of such data, treatment options for children remain limited, particularly for HIV/TB co-infected young children who cannot be given NVP because of interactions between NVP and TB drugs.

Paediatric formulations exist. In early 2008 however, BMS, which markets EFV in Europe, discontinued the manufacture of the 100mg capsule, further limiting options for paediatric patients.

The oral solution, while allowing more flexibility in dosing, must be discarded 30 days after opening, and is not interchangeable on a mg per mg basis with the solid dosage forms. The bioavailability of the oral solution is also less than 70% of the oral dosage forms, and hence a larger dose is required to obtain the same blood levels.

# EMTRICITABINE (FTC)

## GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- WHO guidelines: Indicated for first- and second-line for adults.<sup>6</sup>
- Originator company and product brand name: Gilead, Emtriva.
- First approval by U.S. Food and Drug Administration (FDA): July 2003.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- World sales of originator product: 2010: US\$ 28 million; 2009: \$28 million; 2008: \$31 million; 2007: \$32 million; 2006: \$36 million; 2005: \$47 million; 2004: \$58 million.<sup>128, 129, 130, 131, 132</sup>
- Patents: The basic patent on FTC and lamivudine (3TC) was filed by IAF Biochem in 1990 and is due to expire in 2010. As the molecular structure of FTC and 3TC are very closely related, the same patent covers both these drugs.<sup>133, 134</sup>

Emory University also applied for a series of patents that relate to FTC between 1990 and 1992.<sup>135, 136</sup> These are due to expire between 2010 and 2012. In 2005, Gilead acquired the royalty interest for FTC under a \$525 million agreement with Emory University.<sup>137</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one capsule. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

	Daily dose	Aurobindo	Cipla
Who can access this price?		See annex 2	
FTC 200mg capsule	1	<b>61</b> <b>(0.167)</b>	<b>97</b> <b>(0.267)</b>

## SPOTLIGHT ON ACCESS ISSUES

Emtricitabine (FTC) is not offered as part of Gilead's Access Program and is neither registered nor marketed in developing countries. It is, however, available in co-formulation with tenofovir (TDF) and efavirenz (EFV). It is a widely-used ARV both in first- and second-line regimens.

According to the WHO treatment guidelines, "FTC is an equivalent alternative to lamivudine (3TC) as it is structurally related to 3TC, shares the same efficacy against HIV and hepatitis B virus (HBV) and has the same resistance profile."<sup>6</sup>

FTC or 3TC are also recommended for second-line treatment, to be used with either zidovudine (AZT) or tenofovir (TDF), to which a boosted protease inhibitor (PI) should be added.

The latest WHO 2010 guidelines recommend using TDF with either FTC- or 3TC-containing antiretroviral regimens in all HIV/HBV co-infected individuals needing treatment.<sup>7</sup>

### Patents

Although basic patents on FTC could not be applied for in India because the country did not grant patents on pharmaceuticals at the time, Gilead reported holding patent rights on FTC in 45 other developing countries.<sup>138</sup>

In mid-2006, Gilead signed licensing agreements with generic manufacturers in India, allowing them to manufacture and export generic versions of Gilead's TDF in combination with other ARVs – including FTC – to a limited list of countries, in return for the payment of a 5% royalty.<sup>139</sup>

### Paediatrics

FTC is approved for use in children from three months through to 17 years and has the advantage of once-daily dosing.<sup>140</sup>

Paediatric formulations are available. The solution produced by Gilead is not adapted to developing world needs, however, as it requires refrigeration prior to dispensing and must be used within three months of opening and stored at temperatures below 25°C.

In addition, Gilead offers no reduced pricing for the developing world.

To simplify treatment for all children, there is an urgent need for child-adapted formulations of FTC to be made available, and generic paediatric FTC formulations to be quality-assured by WHO prequalification.



# ENFUVRTIDE

## GENERAL INFORMATION

- Therapeutic class: Fusion inhibitor.
- WHO guidelines: Not currently included in WHO guidelines. Indicated for treatment-experienced adult patients who have evidence of viral HIV-1 replication despite ongoing antiretroviral therapy.<sup>141</sup>
- Originator company and product brand name: Roche and Trimeris, Fuzeon.
- First approval by U.S. Food and Drug Administration (FDA): March 2003.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Not included in the 17th edition.<sup>24</sup>
- World sales of originator product: There are no sales figures listed in the companies' annual report.
- Patents: The basic patent on enfuvirtide was applied for by Duke University in June 1994,<sup>142</sup> and is due to expire in 2014. Duke researchers founded the pharmaceutical company Trimeris,

which began development of enfuvirtide (previously called T-20) in 1996. In 1999, Trimeris entered into partnership with Hoffmann-La Roche to complete the development of the drug. Chiron also owns patents related to processes for producing enfuvirtide,<sup>143</sup> which expired in 2005, but protection has been extended until 2010 in some European countries. A licensing agreement was established between Roche and Chiron in 2004.<sup>144</sup>

## PRICE INFORMATION

**Roche was invited to contribute a price for this publication and communicated that it does not offer a lower price for developing countries and is not planning to offer one in the future.**

## SPOTLIGHT ON ACCESS ISSUES

Enfuvirtide is the first drug developed in the fusion inhibitor class, whose novel mechanism of action prevents the penetration of target cells by the HIV virus. This new drug is predominately used in the developed world as 'salvage therapy' for patients who are already resistant to multiple antiretroviral agents.

Enfuvirtide is formulated as an injection and requires the patient or caregiver to learn how to reconstitute powder vials with sterile water. Since the vials are formulated for single use, the patient or caregiver needs to accurately syringe out the required dose and volume. This makes the drug ill-adapted for use in resource-limited settings.

There is no generic version of this drug yet available and Roche offers no reduced pricing for the developing world. The current price in some developed countries of nearly \$28,000 per patient per year is prohibitive for many developing countries that may have a need for this product.<sup>145</sup>

### Patents

In developing countries such as China and Brazil, Trimeris filed for patents related to methods for synthesizing enfuvirtide, which may run until 2019.<sup>146</sup>

The patent was granted in China.<sup>38</sup>

In Brazil, enfuvirtide is available at \$12,812 ppy.<sup>147</sup>

### Paediatrics

Enfuvirtide is approved for use in children over six years of age.<sup>148</sup> To simplify treatment for all children, there is an urgent need for studies on enfuvirtide to be completed in infants and children under six, and for child-adapted formulations to be made available.

# ETRAVIRINE (ETV)

## GENERAL INFORMATION

- Therapeutic class: Non-nucleoside reverse transcriptase inhibitor (NNRTI).
- WHO guidelines: Listed in the WHO guideline as potential third-line drug.<sup>6</sup> Approved by U.S. Food and Drug Administration (FDA) for treatment experienced adult patients who have evidence of resistance to an NNRTI and other antiretroviral agents.<sup>149</sup>
- Originator company and product brand name: Tibotec (a subsidiary of Johnson & Johnson), Intelence.
- First approval by U.S. Food and Drug Administration (FDA): January 2008.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Not included in the 17th edition.<sup>24</sup>
- World sales of originator product: There are no sales figures listed in the companies' annual report.
- Patents: The basic patent on etravirine was applied for by Janssen Pharmaceutica in 1999 and is due to expire in 2019.<sup>150</sup> In 2006, Tibotec applied for subsequent patents related to novel series of bisaryl substituted pyrimidine derivatives. Both Janssen Pharmaceutica and Tibotec are subsidiaries of Johnson & Johnson.<sup>151, 152</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet.

	Daily dose	Tibotec
Who can access this price?		See annex 2
ETV 100mg tablet	4	913 (0.625)

## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations which for the first time call for the need of third-line therapy. Many studies are ongoing; drugs likely to have anti-HIV activity in third-line regimens are etravirine (ETV), boosted darunavir (DRV), and raltegravir (RAL).<sup>7</sup>

In August 2009, Tibotec (a subsidiary of Johnson & Johnson) signed a royalty-free, non-exclusive licence agreement with Aspen of South Africa covering all of sub-Saharan Africa for all ETV formulations. Under this agreement, Aspen will handle regulatory and distribution activities. At the time of writing, Aspen/Tibotec ETV 100mg tablet is registered in at least six countries in

sub-Saharan Africa with applications in process in sixteen others.

The price of ETV, at \$913 ppy, is prohibitive for developing countries. There is no generic version of this drug yet available.

### Patents

Patents have been applied for widely in the developing world, including in Africa. Janssen Pharmaceutica obtained the molecule patent in India<sup>153</sup> and China.<sup>38</sup>

This patent will block the development of generic formulations of ETV, unless licences – voluntary or compulsory – are issued to generic companies for the manufacture of affordable versions of the drug.

In India, Tibotec has filed additional patent applications<sup>154</sup> on new forms which, if granted, will extend its monopoly in India from 2021 to 2027.

### Paediatrics

ETV is not approved for use in children today. A waiver of paediatric studies from birth to two months was granted by EMA on grounds that the medicine does not represent significant therapeutic benefit over existing treatments.<sup>155</sup>

As few treatment options exist for children with HIV, it is critical that paediatric studies of ETV be completed and adapted formulations be made available.

# FOSAMPRENAVIR (FPV or f-APV)



## GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- WHO guidelines: Not currently included in WHO guidelines.
- Originator company and product brand name: GlaxoSmithKline (GSK) and Vertex Pharmaceuticals, Lexiva. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): October 2003.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Not included in the 17th edition.<sup>24</sup>
- World sales of originator product: There are no sales figures listed in the companies' annual report.
- Patents: The basic patent was applied for by Vertex Pharmaceuticals in March 1998,<sup>156</sup> and due to expire in 2018. Fosamprenavir, a phosphate ester prodrug of amprenavir,<sup>157</sup> was developed and launched by GSK, under licence from Vertex. GSK also holds patents related to a crystalline form of the calcium salt of FPV,<sup>158</sup> due to expire in 2019.

## PRICE INFORMATION

	Daily dose	ViiV
Who can access this price?		See annex 2
FPV 50mg/ml oral suspension	12ml*	837 (0.191/ml)
FPV 700mg tablet	2*	1131 (1.549)

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet/ml of oral suspension.

\*The dose of FPV must be boosted with RTV 100mg twice a day.

## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors (PI), to be taken in combination with two NRTIs. They are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r).<sup>7</sup> As fosamprenavir (FPV) was not identified as one of the priority products, its use will be limited in the developing world.<sup>7</sup>

While FPV/r based regimens show good antiviral efficacy and are generally well tolerated in treatment-naïve patients, the experience of this drug in developed countries is limited and little comparative data is available in treatment-experienced patients.<sup>159</sup>

FPV, like all PIs (with the exception of nelfinavir (NFV)), requires boosting with ritonavir (RTV). Abbott's heat-stable ritonavir received marketing approval in the U.S. and Europe in early 2010. Registering this new

formulation in developing countries will be crucial in order to allow the use of other PIs than lopinavir. A generic heat-stable RTV is now available and was WHO prequalified in late 2010.

In 2011, ViiV clarified their pricing structure (see annex 2), confirming that their differential prices 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 those prices, and will have to negotiate prices on a case-by-case basis.

### Patents

Patent applications have been filed in many developing countries.

In Brazil, the basic patent was rejected by the patent office, although in December 2009 ViiV filed an appeal against the decision.

In China, South Africa, ARIPO and OAPI countries,<sup>160</sup> most patents have been granted.

In June 2010, India granted a patent to Vertex Pharmaceuticals that covers fosamprenavir salts, including calcium which is the marketed salt.<sup>323</sup>

There are no generic formulations of this product available today.

### Paediatrics

FPV was approved for use in children above the age of two in October 2007.<sup>23</sup>

A paediatric suspension is available. However, FPV must be given with a RTV booster, but the RTV solution currently available has a bitter aftertaste and contains 43% alcohol, and is thus not adapted for children, limiting the use of FPV in this population.

# INDINAVIR (IDV)

## GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- WHO guidelines: Not currently included in WHO guidelines.
- Originator company and product brand name: Merck, Crixivan.
- First approval by U.S. Food and Drug Administration (FDA): March 1996.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- World sales of originator product: There are no sales figures listed in the companies' annual report.
- Patents: The basic patent was filed by Merck in 1992 and is due to expire in 2012 in countries granting 20-year patents.<sup>161</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one capsule. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

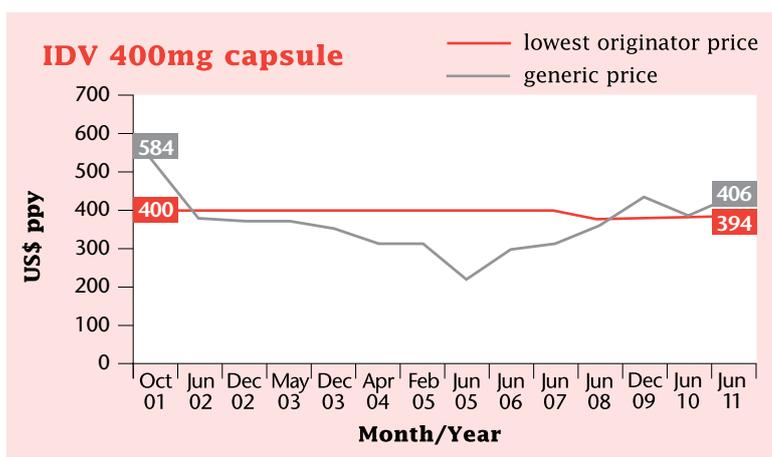
	Daily dose	Merck	Aurobindo	Cipla	Hetero
Who can access this price?		See annex 2 & annex 10**	See annex 2		
IDV 400mg capsule	4*	<b>394 (0.270)</b>	292 (0.200)	422 (0.289)	<b>406 (0.278)</b>

\*The dose of IDV must be boosted with RTV 100mg twice a day.

\*\*For the first time this year, Merck has decided not to give discounted prices to Category 2 countries. See 'Spotlight on access issues' below.

### Evolution of the lowest price quoted for developing countries since 2001:

As of May 2011, two generic sources of IDV 400mg capsule were quality-assured by US FDA or WHO prequalification. Only one of these sources provided prices for this document, and is the one shown here.



## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors (PI), to be taken in combination with two NRTIs. They are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r). As IDV was not identified as one of the priority products, its use will be limited in the developing world.<sup>7</sup>

IDV, like all PIs (with the exception of nelfinavir (NFV)), requires boosting with RTV. Abbott's heat-stable ritonavir received marketing approval in the U.S. and Europe in early 2010. Registering this new formulation in

developing countries will be crucial in order to allow the use of other PIs than lopinavir. A generic heat-stable RTV is now available and was WHO prequalified in late 2010.

Some generic manufacturers have stopped production of IDV, or only manufacture it for specific orders, because of a decrease in demand for this product.

In 2011, Merck ceased offering discounted prices to all lower middle- and upper middle-income countries according to the World Bank Classification (see annex 6 for a list of these countries). The company proposes

instead to negotiate discounted prices on a case-by case basis, based on country income and disease burden.

### Patents

In Brazil, indinavir is one of the ARVs produced locally. The patent application was filed in 1994, at a time when the country did not grant patents on pharmaceuticals, and was therefore rejected.

### Paediatrics

The optimal dosing regimen for the use of IDV in paediatric patients has not been established.<sup>162</sup>

No paediatric formulation exists.



# LAMIVUDINE (3TC)

## GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- WHO guidelines: Indicated for first- and second-line for adults, adolescents and children.<sup>6,22</sup>
- Originator company and product brand name: GlaxoSmithKline (GSK), Epivir. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): November 1995.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- World sales of originator product: 2010: US\$ 186 million; 2009: \$197 million; 2008: \$225 million; 2007: \$309 million; 2006: \$398 million; 2005: \$398 million; 2004: \$549 million.<sup>163, 25, 28, 29, 30</sup>
- Patents: The basic patent on emtricitabine (FTC) and 3TC was filed by IAF Biochem in 1990 and should therefore have expired in 2010 in countries with 20-year patent terms. As the molecular structure of FTC and 3TC are very closely related, the same patent covers both these drugs.<sup>133</sup> GSK obtained a licence from IAF to manufacture 3TC and filed additional patents on new forms of 3TC in 1992, which are due to expire in June 2012.<sup>164</sup> GSK also applied for a new formulation patent in 1998. This patent was granted in Brazil, China and in ARIPO countries.<sup>165</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

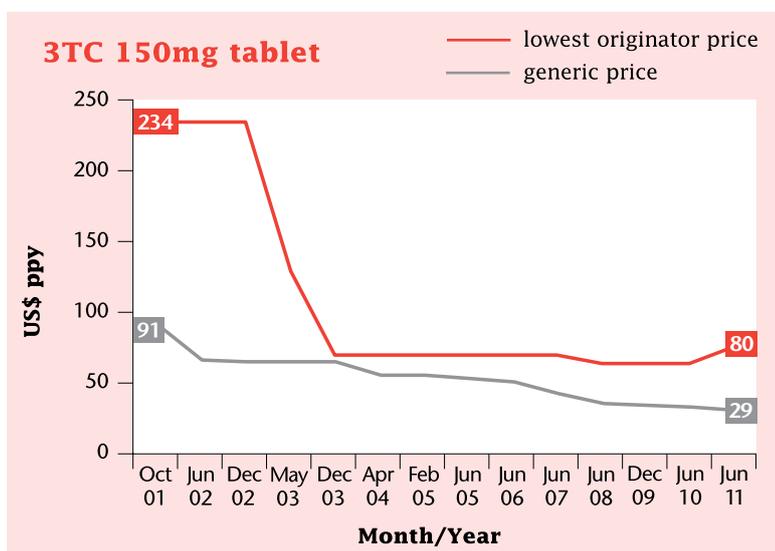
	Daily dose	ViiV	Alkem	Aspen	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Micro Labs	Ranbaxy	Strides
Who can access this price?		See annex 2									
3TC 10mg/ml oral solution	10ml	<b>212 (0.058/ml)</b>		33 (0.009/ml)	<b>29 (0.008/ml)</b>	<b>55 (0.015/ml)</b>	37 (0.010/ml)				
3TC 150mg tablet	2	<b>80 (0.109)</b>	<b>42 (0.058)</b>	<b>29 (0.040)</b>	<b>34 (0.047)</b>	<b>33 (0.045)</b>	<b>33 (0.045)</b>	<b>31 (0.042)</b>	31 (0.042)	<b>34 (0.047)</b>	<b>29 (0.040)</b>
3TC 300mg tablet	1				<b>24 (0.067)</b>	<b>41 (0.113)</b>	<b>38 (0.103)</b>		26 (0.071)		

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest price quoted for developing countries since 2001:

As of May 2011, nine generic sources of 3TC 150mg tablet were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

Since 2001, the originator price has decreased by 66%, while generic prices have dropped by 68%.



## SPOTLIGHT ON ACCESS ISSUES

Lamivudine (3TC) is a widely-used ARV both in first- and second-line regimens. It has been an important component of fixed-dose combinations that have fostered treatment scale-up in resource-limited settings.

According to the WHO treatment guidelines, “FTC is an equivalent alternative to lamivudine (3TC) as it is structurally related to 3TC, shares the same efficacy against HIV and hepatitis B virus (HBV) and has the same resistance profile.”<sup>6</sup>

The latest WHO 2010 guidelines also recommend using TDF with either FTC- or 3TC-containing antiretroviral regimens in all HIV/HBV co-infected individuals needing treatment.<sup>7</sup>

In 2011, ViiV clarified their pricing structure (see annex 2), confirming that their differential prices 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 those prices, and will have to negotiate prices on a case-by-case basis.

In February 2011, Shionogi-ViiV Healthcare announced<sup>36</sup> the start of a phase III trial for a new fixed-dose combination including ABC, lamivudine (3TC) and a new integrase inhibitor S/GSK1349572 (an investigational drug known as dolutegravir, now in phase III clinical development).<sup>37</sup>

### Patents

Generic competition for 3TC originated in countries with manufacturing capacity where the drug is not under patent, such as India, Thailand and Brazil.

### Paediatrics

3TC is approved for use and is widely used in children. In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends 3TC to be given with either ABC, d4T or AZT and either an NNRTI or a PI in the first-line. 3TC can also be part of second-line regimens, depending on what has been used as a first-line. 3TC is part of both of the most commonly used first-line regimens for children today (3TC/d4T/NVP and AZT/3TC/NVP).

Today, once-daily dosing of 3TC is only recommended for patients over 16; more studies are needed to confirm the safety of daily dosing of 3TC in children.<sup>43</sup>

An oral solution of 3TC is available. As of May 2011, two generic sources were quality-assured by either US FDA or WHO prequalification.

Generic manufacturers have been developing both double and triple fixed-dose combinations containing 3TC. As of May 2011, ten sources of paediatric triple FDCs containing 3TC were quality-assured by either US FDA or WHO prequalification. All are produced by generic companies.



# LOPINAVIR/ RITONAVIR (LPV/r)

## GENERAL INFORMATION

- Therapeutic class: Boosted protease inhibitor (PI) in a double fixed-dose combination.
- WHO guidelines: Indicated for second-line, for adults, adolescents and children.<sup>6,22</sup>
- Originator company and product brand name: Abbott, Kaletra/Aluvia.
- First approval by U.S. Food and Drug Administration (FDA): September 2000 (soft-gel capsules); October 2005 (heat-stable tablets).<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- World sales of originator product: 2010: US\$1.26 billion; 2009: \$1.37 billion; 2008: \$1.47 billion; 2007: \$1.32 billion; 2004: \$897 million; 2003: \$754 million; 2002: \$551 million; 2001: \$292 million.<sup>166, 167, 168, 169</sup>
- Patents: Most patents related to ritonavir (RTV) also cover LPV/r. The basic patent related to LPV was applied for by Abbott in 1996.<sup>170</sup> In addition, Abbott applied for patents more specifically related to LPV/r soft-gel capsules in 1997<sup>171</sup> which are due to expire in 2017. An application for a patent on the heat-stable tablet formulation was also filed in 2004,<sup>172</sup> which could potentially run until 2024, in countries where granted.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one capsule / tablet / ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

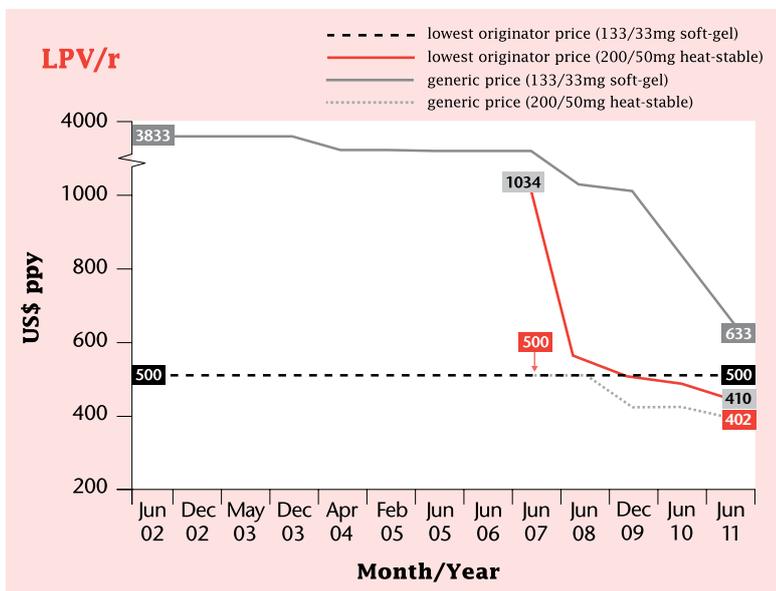
	Daily dose	Abbott		Aurobindo (CF)	Cipla (CF)	Hetero	Matrix (CF)
		Category 1 countries	Category 2 countries				
Who can access this price?		See annex 2 & annex 8		See annex 2			
LPV/r 80/20mg/ml oral solution	4 ml	<b>164 (0.112/ml)</b>	<b>400 (0.274/ml)</b>		256 (0.175/ml)		
LPV/r 100/25mg tablet (heat-stable)	3	<b>153 (0.140)</b>	<b>376 (0.343)</b>	<b>175 (0.160)</b>			<b>164 (0.150)</b>
LPV/r 133/33mg soft-gel capsule (non heat-stable)	6	<b>500 (0.228)</b>	<b>1000 (0.457)</b>		633 (0.289)		
LPV/r 200/50mg tablet (heat-stable)	4	<b>410 (0.281)</b>	<b>1000 (0.457)</b>	<b>438 (0.300)</b>	<b>499 (0.342)</b>	493 (0.338)	<b>402 (0.275)</b>

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest quoted price for developing countries since 2002:

As of May 2011, there was no generic source of LPV/r 133/33mg soft-gel capsule quality-assured by US FDA or WHO prequalification, so the lowest-priced generic is shown in this graph. There were however three quality-assured generic sources of LPV/r 200/50mg heat-stable tablet. The one with the lowest price is shown here.

The generic price of LPV/r 200/50mg heat-stable tablet has decreased by 61% since 2007 and is now lower than originator price.



## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors (PI), to be taken in combination with two NRTIs. They are lopinavir/ritonavir (LPV/r) and atazanavir (ATV) boosted with ritonavir (RTV).<sup>7</sup> With its once-a-day dosing ATV is the more patient-friendly PI of the two.

The heat-stable formulation of LPV/r manufactured by Abbott and Indian generic companies is now marketed in developing countries. In comparison with the older, soft-gel capsule formulation, the new formulation has a lower pill count (reducing the burden from six to four pills per day), there is no need for refrigeration, and there are no dietary restrictions. It is now approved as once-a-day dosing in treatment-experienced patients with fewer than three lopinavir resistance-associated mutations.<sup>23</sup> This should enhance adherence. However, pill burden remains an issue.

The entry of generic manufacturers is having a positive effect on the market, and prices are declining. However Abbott's sales of this drug dominates the developing world where it captured 81% of the market share in 2008.<sup>16</sup>

However, for the first time, the most affordable quality-assured generic price of LPV/r 200/50mg tablet is lower than Abbott's price at \$402ppy.

### Patents

In India, Abbott has applied for several patents on the polymorphic forms of LPV<sup>173</sup> and RTV,<sup>174, 175, 176, 177</sup> on the combination of LPV/r in a tablet formulation,<sup>178, 179</sup> and on the LPV process. A number of these applications have been opposed

by civil society organisations<sup>180</sup> and generic companies.

Following a pre-grant opposition to the application related to the tablet formulation of LPV/r, the application was rejected by the Indian patent office.<sup>181</sup> While an appeal is pending to the rejection, Abbott has abandoned the two divisional patent applications it had filed on the tablet formulation of LPV/r.<sup>182, 183</sup> The Indian patent office also rejected a patent application on lopinavir crystalline polymorphs.<sup>184</sup>

In a welcome move, Abbott has also abandoned several applications including the divisional on the RTV crystalline polymorph. However, key applications, relating to the RTV stable polymorph,<sup>185</sup> the solid pharmaceutical dosage (tablet) formulation of LPV/r,<sup>179</sup> and to the LPV process<sup>186</sup> are still pending before the Indian patent office. If one of these patent applications is granted, current generic competition, which is bringing prices substantially down as demand increases, will be under threat. India and other countries could urgently issue compulsory licences to enable unrestricted competition from generic manufacturers to continue.

In Thailand, where Abbott holds patents, the price of LPV/r was \$2,200 ppy in 2007. In January 2007, the Ministry of Public Health issued a compulsory licence to import more affordable generic versions of the drug from India.<sup>124</sup> Thailand faced fierce criticism from developed countries and multinational pharmaceutical companies and Abbott's response was to withdraw all registration applications in Thailand

for its new products, including the heat-stable LPV/r. Thailand today imports generic LPV/r from India for \$793 ppy.<sup>125</sup>

In response to Thailand's compulsory licence, Abbott reduced the price for 40 middle-income countries for both the soft-gel and the heat-stable version to \$1,000 ppy, including Brazil which at the time was paying \$1,380.<sup>3</sup>

The basic patent for LPV/r is protected in Brazil under the so-called 'pipeline mechanism', a provision in Brazilian patent law deemed to be in excess of the minimum standards for intellectual property protection under the TRIPS Agreement. In 2007, the National Federation of Pharmacists (Fenafar) – on behalf of the Brazilian Network for the Integration of Peoples (Rebrip) – made a request to the Brazilian Prosecutor General to consider overturning the pipeline mechanism on the grounds that it is unconstitutional. A key argument in favour of overturning the mechanism is that these patents should not be granted in Brazil, since they were already in the public domain and that granting the patents in this way is against the public interest. In 2009, the Prosecutor General lodged a case for unconstitutionality with the Supreme Court.<sup>187</sup> MSF-Brazil is actively following the case.<sup>188</sup>

In 2005, the Brazilian government entered into negotiations with Abbott to reduce the price of LPV/r and in June of the same year, the Ministry of Health declared the drug to be of public interest, which is the first step towards issuing a compulsory licence. However, in October 2005 an agreement between Abbott and the government was signed.

## SPOTLIGHT ON ACCESS ISSUES

The deal included clauses such as an obligation not to issue a compulsory licence. Civil society groups considered this agreement a huge setback<sup>189</sup> and filed a civil public action against Abbott and the government demanding that a compulsory licence be issued.<sup>190</sup> The case received a negative preliminary decision, in which it was said that Brazil should not “break patents” since the country was included in the US government’s priority watch list for infraction of IP rules.<sup>191</sup> The civil public action is still awaiting final judgment.

In 2006, civil society groups also filed an opposition contesting a divisional patent application for LPV/r filed by Abbott.<sup>192</sup> As the first patent was granted through the pipeline mechanism, it was argued that there is no legal provision for divisional applications of pipeline patents. In July 2010, the divisional patent application was rejected by the Brazilian Patent Office (INPI).

The patent issued through the pipeline mechanism in Brazil covers the compound and the soft-gel capsule until 2017. However, at least two other patent applications for the tablet formulation are under analysis at INPI.<sup>193</sup> If they are granted, Abbott’s monopoly may be extended until 2026.

### Paediatrics

LPV/r is approved for use in children from two weeks old.<sup>23</sup>

Recent changes in the WHO guidelines recommending that all HIV-positive children under one year of age start ARV therapy as soon as possible regardless of clinical status, combined with the recommendation to start all children exposed to nevirapine on a PI-based regimen, should result in an increased demand for this combination for very young children.<sup>194, 113</sup>

Paediatric formulations exist. In early 2007, Abbott released a paediatric LPV/r 100/25mg heat-stable tablet. As of May 2011, two generic sources of heat-stable LPV/r 100/25mg were quality-assured by either US FDA or WHO prequalification. While this formulation is welcome, it does not help the youngest patients, as the tablet is 15mm long and cannot be crushed, leaving this formulation unsuitable for children who cannot swallow tablets.

The alternative for these young children is a solution that requires refrigeration until dispensing, after which it must be stored below 25°C for no more than six weeks. Furthermore, the solution consists

of 42% alcohol and has a very unpleasant taste. In addition, safety concerns were raised in March 2011 when US FDA revised labelling to warn against the use of LPV/r solution in premature babies until 14 days after their due date, after serious health problems had been reported in premature babies.<sup>195</sup>

There is an urgent need for more adapted heat-stable paediatric formulations of LPV/r (such as soluble granules or sprinkles) for young children who can not swallow the existing tablet. A heat-stable sprinkle in a paediatric dose is under development by generic companies. The Paediatric Antiretroviral Working Group of WHO considers the development of a LPV/r 40/10mg heat-stable sprinkle to be a high priority.<sup>22</sup>

# MARAVIROC (MVC)

## GENERAL INFORMATION

- Therapeutic class: Chemokine co-receptor 5 (CCR5) antagonist (entry inhibitor).
- WHO guidelines: Not currently included in WHO guidelines. Indicated for treatment-experienced adult patients infected with only CCR5 tropic HIV-1 detectable strains, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.<sup>196</sup>
- Originator company and product brand name: Pfizer, Selzentry (US) and Celsentri (Europe). In April 2009, Pfizer and GlaxoSmithKline jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): August 2007.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Not included in the 17th edition.<sup>24</sup>
- World sales of originator product: There are no sales figures listed in the company's annual report.
- Patents: The basic patent was applied for by Pfizer in December 1999<sup>197</sup> and is due to expire in 2019. Pfizer also owns an additional patent more specifically related to crystalline maraviroc,<sup>198</sup> which may run up to 2021.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet.

	Daily dose	ViiV
Who can access this price?		See annex 2
MVC 150mg tablet	4*	1584 (1.085)

\*The dose is dependent on concurrent administered medications.

## SPOTLIGHT ON ACCESS ISSUES

Maraviroc (MVC) is classed as a CCR5 co-receptor antagonist that targets the penetration of cells by the HIV virus. This drug option is predominately used in the developed world as 'salvage therapy' for patients who are already resistant to multiple drug classes. Not all patients will benefit from this drug, as only some HIV viruses use this CCR5 co-receptor.

The recommendation is for patients to have a tropism test to look for this co-receptor prior to treatment. In developing countries, where basic laboratory monitoring is not always available, the reality of this type of testing being available is limited. Today, this test is not widely available and is expensive, costing approximately \$1,900.<sup>199</sup>

In 2011, ViiV clarified their pricing structure (see annex 2), confirming

that their differential prices 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 those prices, and will have to negotiate prices on a case-by-case basis.

### Patents

Pfizer obtained a patent in India in 2007.<sup>200</sup> This patent blocks the manufacture of generic formulations of MVC in India, limiting the much-needed competition that historically has been shown to lead to price reductions.

An Indian pharmaceutical company, Natco Pharmaceuticals reportedly sent a notice for a voluntary licence to Pfizer in November 2010 seeking to manufacture and sell its generic MVC at about one-fifth the price.<sup>201</sup>

If negotiations with Pfizer fail, Natco can seek a compulsory licence under the terms of the Indian patent law.

Pfizer has applied for product patents and patents for the crystal form in Brazil, South Africa, India, China, ARIPO<sup>202</sup> and OAPI countries.<sup>203</sup> To date, patents on the crystal form have been granted in India,<sup>204,205</sup> China, and in ARIPO and OAPI countries.

### Paediatrics

The safety and efficacy of MVC in patients under 16 years of age have not been established.

As few treatment options exist for children with HIV, it is critical that paediatric studies of MVC be completed and adapted formulations be made available.



# NELFINAVIR (NFV)

## GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- WHO Model List of Essential Medicines (EML): Not included in the 17th edition.<sup>24</sup>
- Patents: The basic patent was applied for in 1994 by Agouron Pharmaceuticals Inc.,<sup>207</sup> and is due to expire in 2014. Agouron Pharmaceuticals is now a subsidiary of Pfizer. NFV was developed by Agouron as part of a joint venture with Japan Tobacco, Inc. NFV is supplied by Roche outside the U.S., Canada and Japan.<sup>208</sup>
- WHO guidelines: Not currently included in WHO guidelines.
- World sales of originator product: 2004: US\$ 259 million. After 2004, there are no sales figures listed in the company's annual report.<sup>206</sup>
- Originator company and product brand name: Roche, Viracept.
- First approval by U.S. Food and Drug Administration (FDA): March 1997.<sup>23</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

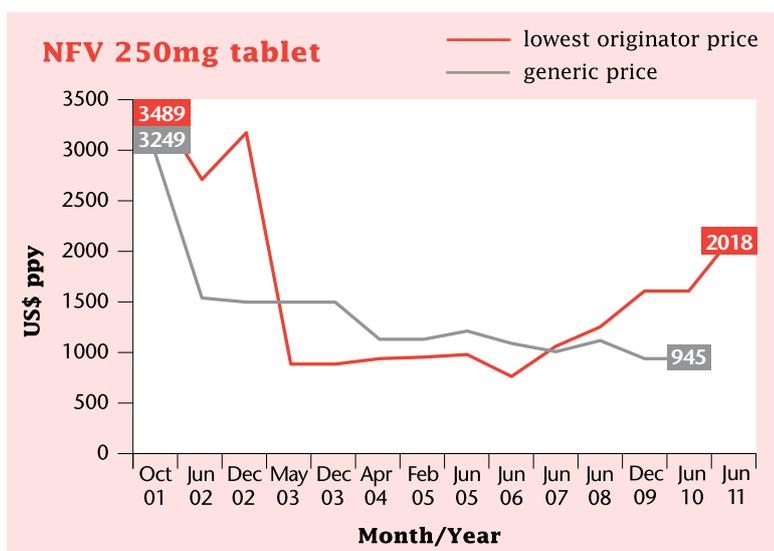
The price in brackets corresponds to the price of one tablet/gram of oral powder. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

	Daily dose	Roche	
		Category 1 countries	Category 2 countries
Who can access this price?		See annex 2	
NFV 50mg/g oral powder	24g	<b>2742</b> <b>(0.313/g)</b>	<b>3171</b> <b>(0.362/g)</b>
NFV 250mg tablet	10	<b>2018</b> <b>(0.553)</b>	<b>3132</b> <b>(0.858)</b>

### Evolution of the lowest quoted price for developing countries since 2001:

For the first time since 2001, no generic companies provided prices this year for nelfinavir 250mg tablet for this publication.

After a sharp decrease of the price of the originator between 2002 and 2003, this price has then steadily increased every year since 2006, by a total of 166%.



## SPOTLIGHT ON ACCESS ISSUES

Nelfinavir (NFV) is the only protease inhibitor (PI) that does not require boosting with ritonavir (RTV).

The large pill burden (10 tablets a day for an adult) and its high price make it a less-desirable option when selecting a PI.

In June 2007, Roche recalled all batches of NFV due to high levels of Ethyl Methane Sulphonate (EMS), a by-product of the manufacturing process and a known carcinogen in animals. Roche's marketing licence for NFV was suspended in Europe and WHO Prequalification temporarily suspended the product. In September 2007, the suspensions were lifted and marketing licences reinstated.<sup>209</sup> As a result of the recall, many patients were changed to

another PI. The recall highlights the risks associated with relying on a single producer for a medicine.

It is unknown if there will continue to be demand for the NFV formulation in the future. NFV was also deleted from the 16th edition of the WHO Model List of Essential Medicines (EML).

### Patents

Although basic patents on NFV could not be applied for in India because the country did not grant patents on pharmaceuticals at the time, Agouron applied for patents in many other developing countries. This factor contributes to the high price of the drug, together with the small demand.

### Paediatrics

In 1997, NFV was approved for use in children.<sup>210</sup>

The use of NFV oral powder in children is extremely complex. To obtain the correct dose for a 10kg child, 12g of the oral powder must be mixed with water. Access to clean, safe water is often not assured in all developing countries.

Not only is the paediatric NFV formulation ill-adapted, but its price remains prohibitive.



# NEVIRAPINE (NVP)

## GENERAL INFORMATION

- Therapeutic class: Non-nucleoside reverse transcriptase inhibitor (NNRTI).
- WHO guidelines: Indicated for first- and second-line for adults, adolescents and children.<sup>6,22</sup>
- Originator company and product brand name: Boehringer Ingelheim (BI), Viramune and Viramune XR.
- First approval by U.S. Food and Drug Administration (FDA): June 1996.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- World sales of originator product: 2007: US\$ 412 million; 2006: \$370 million; 2005: \$386 million; 2004: \$378 million.<sup>211, 212, 213, 214</sup> After 2007, there are no sales figures quoted in the company's annual report.
- Patents: The basic patents on NVP were applied for by BI in November 1990, and expired in November 2010.<sup>215</sup> BI also holds patents on the hemihydrate form of NVP, used in the suspension in 1998, which are due to expire 2018.<sup>216</sup> Additionally, BI applied for a patent on the extended release formulation of nevirapine in 2008, which is due to expire in 2028.<sup>217</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet/ml of suspension. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

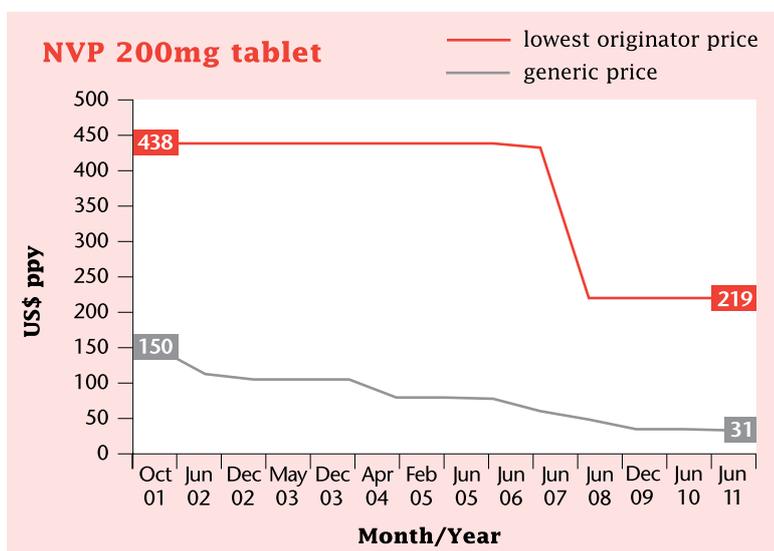
	Daily dose	Boehringer Ingelheim		Aspen	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy	Strides
		Category 1 countries	Category 2 countries							
Who can access this price?		See annex 2								
NVP 10mg/ml suspension	20 ml	<b>380</b> (0.052/ml)	<b>533</b> (0.073/ml)		<b>58</b> (0.008/ml)	<b>110</b> (0.015/ml)				
NVP 200mg tablet	2	<b>219</b> (0.300)	<b>438</b> (0.600)	<b>37</b> (0.051)	<b>37</b> (0.050)	<b>39</b> (0.054)	<b>37</b> (0.050)	<b>31</b> (0.043)	<b>37</b> (0.050)	<b>32</b> (0.044)

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest price quoted for developing countries since 2001:

As of May 2011, 10 generic sources of NVP 200mg tablet were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

Although the originator price dropped by 50% in 2007, the generic price has decreased by almost 80% since 2001, and today is approximately 14% of the originator price.



## SPOTLIGHT ON ACCESS ISSUES

Nevirapine (NVP) is a widely-used ARV, predominately in first-line regimens. It has been an important component of the fixed-dose combinations that have fostered treatment scale-up in resource-limited settings.

However NVP interacts with one of the most commonly used TB drugs, rifampicin, requiring a patient to switch to EFV during the course of TB treatment.

The price of NVP has decreased dramatically over the past years as a result of generic competition.

An extended release formulation of NVP was approved by the US FDA in March 2011, shortly after the patent expiry of NVP worldwide.<sup>218</sup> While it offers once a day dosing, a lead in dose of 200mg once daily is still required for the first 14 days for patients newly started on NVP. It will remain as a stand-alone tablet due to the specific slow release property in this formulation.

### Patents

Boehringer Ingelheim obtained the basic patent on NVP in several developing countries, but no patent could be obtained in countries such as India, Brazil, China or Thailand, which were not granting patents on medicines at the time. Many developing countries, where NVP is under patent, import generic versions of NVP by making use of TRIPS flexibilities. The basic patent expired in many countries in 2010.

However, after India introduced patent protection for pharmaceutical products in 2005, BI applied for a patent on the hemihydrate form of NVP, which relates to the paediatric

suspension. Civil society groups filed a pre-grant opposition to BI's application in May 2006. In June 2008, the application was rejected by the Indian patent office, allowing for unrestricted competition on the paediatric formulation. This constituted an important victory for Indian civil society, as this was the first patent application related to a HIV medicine to have been rejected as a result of a pre-grant opposition process, in accordance with the 2005 Indian Patents Act.<sup>219</sup>

In 2008, BI filed a PCT application<sup>220</sup> for an extended release formulation of NVP – in India the same application was published in 2010.<sup>221</sup> This application relates to the once a day dosing of NVP.

In African countries, low-income countries and least-developed countries BI has a non-assert policy for its patents, which overcomes some of the barriers to generic competition, but only for the countries concerned. Many developing countries in Asia, Latin America and the Caribbean are excluded from the policy.

### Paediatrics

NVP is approved for use and is widely used in children. In 2010, WHO issued updated guidelines for antiretroviral use in paediatric HIV infection. These guidelines recommend that children under three be given two NRTIs plus nevirapine (to be replaced with lopinavir/ritonavir in case of peripartum nevirapin exposure); for children > 3 years the recommended regime is two NRTIs plus efavirenz (or lopinavir/ritonavir).

NVP is part of both of the most commonly used first-line regimens for children today (3TC/d4T/NVP and AZT/3TC/NVP). With both of these regimens, there is a need to start NVP at a lower dose for the first two weeks to minimise the side effects. This can be done by giving one tablet of a double FDC and one tablet of a triple FDC once a day.

With the increased prevalence of TB/HIV co-infection, there is a need for further studies into the interactions between NVP and the TB drugs rifampicin and rifabutin in children.<sup>199</sup> For this reason, it is critical to have EFV studied for use in children below three years of age.

An oral suspension is available. As of May 2011, two generic sources were quality-assured by either US FDA or WHO prequalification. One generic source of NVP 50mg tablet is quality-assured by US FDA.

The WHO Paediatric Antiretroviral Working Group suggests a new formulation of NVP 20mg scored tablet be developed for the new WHO PMTCT guidelines for infant prophylaxis.<sup>22</sup>

Generic manufacturers have been developing triple fixed-dose combinations including NVP, and as of May 2011, three paediatric triple FDCs that include NVP were quality-assured by either US FDA or WHO prequalification. All are produced by generic companies.



# RALTEGRAVIR (RAL)

## GENERAL INFORMATION

- Therapeutic class: Integrase inhibitor.
- WHO guidelines: Listed in the WHO guideline as potential third-line drug.<sup>6</sup>
- Indication: Indicated for treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.<sup>222</sup>
- Originator company and product brand name: Merck, Isentress.
- First approval by U.S. Food and Drug Administration (FDA): October 2007.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Not included in the 17th edition.<sup>24</sup>
- World sales of originator product: 2010: US\$ 1.09 billion; 2009: \$752 million; 2008: \$361 million; 2007: \$41 million.<sup>223, 224, 225</sup>
- Patents: The basic patent was applied for in October 2002 by the Institute for Research in Molecular Biology (IRBM), Pomezia, Italy, one of Merck's research sites.<sup>226</sup> The patent is due to expire in 2022. In 2005, Merck and IRBM applied for another patent on the potassium salt of RAL which can run up to 2025.<sup>227</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet.

	Daily dose	Merck
Who can access this price?		See annex 2 & annex 10*
RAL 400mg tablet	2	<b>675 (0.925)</b>

\*For the first time this year, Merck decided not to give discounted prices to Category 2 countries. See 'Spotlight on access issues' below.

## SPOTLIGHT ON ACCESS ISSUES

Raltegravir (RAL) is the first of a new class of drugs integrase inhibitors, which has a novel mechanism of action and no apparent cross-resistance with other ARVs. This new drug option will be very important for patients who are treatment-experienced and may already be resistant to multiple antiretroviral agents.

RAL, unlike most drugs from the protease inhibitors class, does not require boosting with ritonavir (RTV).

In 2010, WHO released new recommendations which for the first time call for the need of third-line therapy. Many studies are ongoing – drugs likely to have anti-HIV activity in third-line regimens are RAL, etravirine (ETV), and boosted darunavir (DRV).<sup>7</sup>

Price remains an issue. The lowest price offered by Merck for some countries (see annex 10) is extremely high and unaffordable for developing countries. In 2011, Merck ceased offering discounted prices to all lower middle- and upper middle-income countries according to the World Bank Classification (see annex 6 for a list of these countries). The company proposes instead to negotiate discounted prices on a case-by case basis, based on country income and disease burden. This is concerning for the affordability of products in middle-income countries, especially given the extremely high prices charged in wealthy countries, at \$8,000.<sup>228</sup>

There is no generic raltegravir available.

### Patents

Merck and IRBM applied for international patent applications<sup>229, 230, 231</sup> under the Patent Cooperation Treaty (PCT) that facilitated the filing of these patent applications in many PCT member states, including some developing countries with generic drug manufacturing capacity, like Brazil, China, India and South Africa. IRBM was granted a patent in India in December 2007 which will not expire until 2022.<sup>232</sup> In India, an application on potassium salt of RAL<sup>233</sup> is also pending review before the Indian patent office and warrants a pre-grant opposition. If granted, Merck's monopoly in India will be extended by an additional five years to 2027.

In Brazil, the Ministry of Health has announced that it is working on a technology transfer agreement with Merck for RAL.<sup>234</sup> In 2010, the Brazilian government was paying \$5,870 ppy, a price that is expected to decrease with the technology transfer to \$4,000 in 2015.<sup>235</sup> This approach – which is unlikely to ensure that prices are reduced to a level that is possible through unrestricted generic competition – may well establish a precedent for accessing other newer medicines in the future, both in Brazil and beyond.

As Brazil has one of the oldest HIV patient cohorts in developing countries, the need to access newer HIV medications is occurring earlier than in many other countries. The

access challenges Brazil experiences today will be faced by other developing countries in coming years, and Brazil's actions to improve the accessibility and affordability of RAL and other newer medications will have wider implications for all developing countries. Price reductions achieved by Brazil will set a target price for other countries, especially for other middle- and lower middle-income countries.

The size of Brazil's cohort is also critical. With approximately 4,450 people taking RAL, the country is one of the largest developing country consumers of the medicine,<sup>82</sup> and could thus stimulate an international generic market where prices are reduced through competition and economies of scale.

In India, Merck is charging \$2,500 ppy.<sup>236</sup>

### Paediatrics

The safety and efficacy of RAL in patients under 16 years of age have not been established.<sup>237</sup>

Paediatric studies are ongoing in children from four weeks old.<sup>238</sup> As few treatment options exist for children with HIV, it is critical that paediatric studies of RAL be completed and adapted formulations be made available.



# RILPIVIRINE (TMC 278)

## GENERAL INFORMATION

- Therapeutic class: Non-nucleoside reverse transcriptase inhibitor (NNRTI).
- WHO guidelines: Not currently included in WHO guidelines.
- Originator company and product brand name: Tibotec (a subsidiary of Johnson & Johnson), Edurant.
- First approval by U.S. Food and Drug Administration (FDA): 20 May 2011.<sup>239</sup>
- WHO Model List of Essential Medicines (EML): Not included in the 17th edition.<sup>24</sup>
- Janssen Pharmaceutica filed patents on rilpivirine in 2002 which are due to expire in 2022. Tibotec, one of the companies that compose the Janssen Pharmaceutical companies of Johnson & Johnson, further developed the drug and is now selling and managing it.<sup>24</sup>

## PRICE INFORMATION

**Tibotec and generic companies were invited to contribute a price for this publication and communicated that they do not offer a lower price for developing countries.**

## SPOTLIGHT ON ACCESS ISSUES

Rilpivirine is approved for use in HIV-1 treatment-naïve patients in combination with other antiretrovirals.

The registration of rilpivirine in developing countries will be crucial for accessing the drug in the developing world. However, due to the complexities of use at the approved dose and interactions with TB drugs, it is uncertain<sup>240</sup> to what extent rilpivirine will be useful for resource-limited settings.

Indeed, the approved dose of 25mg once a day comes with a heightened risk of virological failure when starting therapy for patients with high viral loads (>100,000 copies/ml). TMC 278 is also less robust compared to efavirenz. More research is needed to determine the safety and efficacy of higher doses.<sup>241</sup>

### Patents

Without patent barriers blocking generic manufacture in developing countries, rilpivirine could be

produced for as little as \$10 per patient per year. Although questions need to be surmounted concerning its lack of efficacy for patients starting at higher viral load and interactions with TB drugs, its usefulness in resource-limited settings comes from its potential for use in long-acting formulations, and its potential low price.

However patents and patent applications filed by two companies – Janssen Pharmaceutica and Tibotec – are preventing generic production.

Janssen Pharmaceutica applied for a basic patent on rilpivirine in 2003 in PCT,<sup>244,245</sup> which was granted in Africa<sup>246</sup> and countries like South Africa,<sup>247</sup> China<sup>248</sup> and India<sup>249</sup> and is under review in countries like Brazil.<sup>250</sup> In addition, Tibotec applied for a patent in PCT<sup>251</sup> that covers the combinations of rilpivirine/3TC/TDF and rilpivirine/FTC/TDF. This application is now pending review in Brazil<sup>252</sup> and India<sup>253</sup> and

warrants a pre-grant opposition to prevent the extension of the patent monopoly by several years.

In 2010, Tibotec (now a subsidiary of Johnson & Johnson) signed voluntary licence (VL) agreements with generic producers to manufacture, market and distribute rilpivirine and its fixed-dose combination with other ARVs. Indian generic companies – Hetero, Emcure and Matrix – who signed the VL can manufacture and sell in India and to the countries listed in the VL (sub-Saharan Africa, Afghanistan, Bangladesh, Bhutan, Cambodia, Haiti, Kiribati, Laos, Maldives, Myanmar, Nepal, Samoa, Solomon Islands Timor-Leste, Tuvalu, Vanuatu, and Yemen). Aspen will have rights to market the product in sub-Saharan Africa including South Africa.<sup>242,243</sup>

But the benefits will not be felt in Latin America, Central Asia and most Caribbean and South

*Continued above right*

⋮ *Continued from below left*

East Asian countries as they are ineligible to receive generic versions of the medicine under Tibotec's agreement.<sup>254</sup> Among the middle-income countries with significant disease burden, besides India only South Africa can be supplied with the generic version.

Given these restrictive licensing policies, these countries may not be able to import generic versions from Indian companies, even if they override patents in their countries through compulsory licences.

Other conditions of the VL that impact the price or availability of rilpivirine can only be analysed once the terms of the VL are made public.

### **Paediatrics**

The safety and efficacy of rilpivirine in paediatric patients have not been established. Studies are ongoing from 12 years old.<sup>255</sup>

As few treatment options exist for children with HIV, it is critical that paediatric studies of rilpivirine be completed and adapted formulations be made available.



# RITONAVIR (r or RTV)

## GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- WHO guidelines: Indicated for second-line as a booster, for adults, adolescents and children.<sup>6,22</sup>
- Originator company and product brand name: Abbott, Norvir.
- First approval by U.S. Food and Drug Administration (FDA): March 1996 for the oral solution and June 1999 for capsules.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- World sales of originator product: 2004: US\$ 194 million; 2003: \$93 million; 2002: \$122 million.<sup>256</sup> After 2004, there are no sales figures listed in the company's annual report.
- Patents: The basic patent was applied for by Abbott in 1993.<sup>257</sup> Subsequently, Abbott applied for patents related to polymorphic forms of RTV<sup>171,258</sup> and to a soft-gel capsule formulation.<sup>259</sup> These are due to expire respectively in 2019 and 2020.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one capsule / tablet / ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

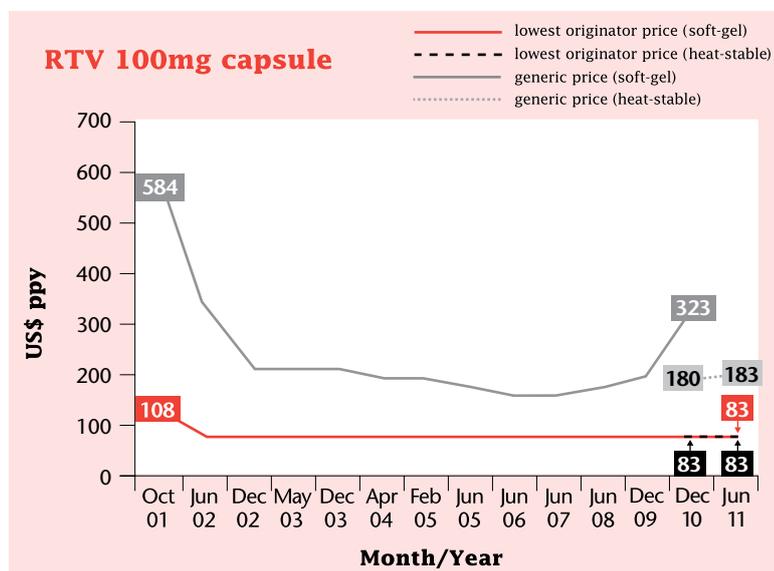
	Daily dose	Abbott		Matrix (CF)
		Category 1 countries	Category 2 countries	
Who can access this price?		See annex 2 & annex 8		See annex 2
RTV 80mg/ml oral solution	-	<b>(0.093/ml)</b>	No discounted price	
RTV 100mg soft-gel capsule (non heat-stable)	2*	<b>83 (0.114)</b>	No discounted price	
RTV 100mg tablet (heat-stable)	2*	<b>83 (0.114)</b>	No discounted price	<b>183 (0.250)</b>

\* Dosing frequency depending on which drug ritonavir is used with as a booster.

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest price quoted for eligible developing countries since 2001:

As of May 2011, one generic source of RTV 100mg heat-stable tablet was quality-assured by WHO prequalification. Its price is shown here.



## SPOTLIGHT ON ACCESS ISSUES

Ritonavir (RTV) is of crucial importance for the scaling-up and management of second-line treatment, as all protease inhibitors (PI) (with the exception of nelfinavir (NFV)), must be boosted with this drug.

Abbott developed a heat-stable fixed-dose combination of lopinavir and RTV (LPV/r) that was approved in the U.S. in 2005. However, it took until early 2010 – 12 years after its RTV soft-gel capsule first received regulatory approval – for Abbott to receive U.S. FDA and EMA approval for a heat-stable stand-alone RTV 100mg tablet.

The market authorisation of a heat-stable version of ritonavir as a separate pill finally put an end to the stranglehold by Abbott on the treatment options available to people living with HIV/AIDS. As a result of Abbott's inaction, many people living with HIV have been deprived of additional, improved and vital treatment options for many years. It also brought to an end the medical double standards the company has promoted by failing to prioritise the development of safer versions of its medicines.

The registration of this new formulation in developing countries will be crucial to allow the use of other PIs than LPV.

For the first time, a generic heat-stable RTV 100mg tablet was WHO prequalified in December 2010.

### Patents

The basic patent on RTV could not be applied for in India as the country did not grant patents on medicines at the time. Nevertheless, Abbott has filed a number of patent applications and divisional applications on new forms of RTV that are pending before the Indian patent office.<sup>174, 175, 176, 177</sup> A pre-grant opposition to an application related to a polymorph of RTV<sup>260, 261</sup> was filed by civil society organisations in India in September 2006.<sup>180</sup> The outcome of this opposition will be crucial to the management of PI-based second-line treatment throughout the developing world.

Abbott abandoned a 2001 patent application including its divisionals on the RTV crystalline polymorph.<sup>262</sup> However, another relating to the RTV stable polymorph is still pending before the Indian patent office and warrants a pre-grant opposition to safeguard generic production.

Patents related to polymorphic forms of RTV have also been filed in other middle-income countries such as China and Brazil where they are pending. In Brazil, RTV is locally produced, as the basic patent is being opposed by Brazilian generic manufacturers in the courts.

In April 2010, Ecuador issued its first compulsory licence allowing Eskegroup SA, the local distributor

for Cipla, to manufacture, offer for sale, sell, use or import RTV, or compositions including RTV, for public non-commercial use, against the payment of royalties to Abbott, until the patent expiration date in 2014.<sup>264</sup> The compulsory licence followed a decree by President Rafael Correa in October 2009, declaring access to essential medicines to be in the public interest of the population and allowing the national intellectual property office to issue compulsory licences to this end, based on Article 31 of the TRIPS Agreement.<sup>265</sup>

According to the Ministry of Health, the compulsory licence already has yielded savings of \$150,000.

### Paediatrics

RTV is approved for use in children from one month of age.<sup>266</sup>

A liquid formulation is available. However, the solution has a bitter aftertaste and contains 43% alcohol, and hence is not adapted for children. This limits the use of all protease inhibitors which require boosting with RTV and do not come in a paediatric fixed-dose combination.

The Paediatric Antiretroviral Working Group of WHO considers the development of a RTV 50mg heat-stable sprinkle or tablet to be a high priority.<sup>22</sup>



# SAQUINAVIR (SQV)

## GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- WHO guidelines: Not currently included in WHO guidelines.
- Originator company and product brand name: Roche, Invirase.
- First approval by U.S. Food and Drug Administration (FDA): December 1995.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- World sales of originator product: There are no sales figures listed in the company's annual report.
- Patents: The basic patent was applied for by Roche in 1990<sup>267</sup> and should have expired in countries not granting patent extensions. A patent related to oral dosage form was applied by Roche in 2004 and is due to expire in 2024.<sup>268</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one capsule / tablet. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

	Daily dose	Roche	
		Category 1 countries	Category 2 countries
Who can access this price?		See annex 2	
SQV 200mg hard capsule	10*	<b>1566 (0.429)</b>	<b>3132 (0.858)</b>
SQV 500mg tablet	4*	<b>1435 (0.983)</b>	<b>3130 (2.144)</b>

\*The dose of SQV must be boosted with RTV 100mg twice a day.

## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors (PI), to be taken in combination with two NRTIs. They are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ ritonavir (LPV/r). As saquinavir (SQV) was not identified as one of the priority products, its use in the developing world will be limited.<sup>7</sup>

SQV, like all PIs (with the exception of nelfinavir (NFV)), requires boosting with ritonavir (RTV). Abbott's heat-stable ritonavir received marketing approval in the U.S. and Europe in early 2010. Registering this new formulation in developing countries will be crucial in order to allow the use of other PIs than lopinavir.

A generic heat-stable RTV is now available and was WHO prequalified in late 2010.

SQV/r appears to be slightly less potent than other boosted PIs and in the original formulation has a high pill count (10 capsules).<sup>159</sup> In 2004, Roche marketed a 500mg tablet of SQV in the U.S. that reduced the pill count from 10 tablets to four. While this new formulation should improve adherence, it is only registered and marketed in selected developing countries.

As with other protease inhibitors, the high price of SQV continues to be a barrier. Solid competition and economies of scale among producers are minimal, as its use is fairly limited.

### Patents

The basic patent was rejected in Brazil where this medicine is locally produced. It was however granted in many other countries including China, South Africa and OAPI countries.

Patents related to the oral dosage form are pending in Brazil and China and have been granted in South Africa.

In India, three patents<sup>269, 270, 271</sup> on improved compositions and SQV mesylate have been granted, blocking generic production till 2024.

### Paediatrics

SQV has not been approved for use in children in the US.

No paediatric is formulation available.

# STAVUDINE (d4T)

## GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- WHO guidelines: Indicated for first-line for children. WHO 2009 guidelines also recommended to move away from d4T first-line in adults and adolescents.<sup>6,22</sup> WHO updated the 2006 guidelines to recommend a reduction in dose of d4T 40mg to d4T 30mg for all weight categories of patients.<sup>22</sup>
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Zerit.
- First approval by U.S. Food and Drug Administration (FDA): December 1994.<sup>23</sup>
- World sales of originator product: 2006: US\$ 155 million; 2005: \$216 million; 2004: \$272 million; 2003: \$354 million. After 2006, there are no sales figures listed in the company's annual report.<sup>48,100</sup>
- Patents: d4T was the result of U.S. public sector research. It was originally synthesised by the Michigan Cancer Foundation in 1966 under a grant from the National Cancer Institute.<sup>273</sup> Researchers from Yale University then discovered its antiretroviral activity and applied for a patent in December 1987, mostly in developed countries, for the use of d4T to treat patients infected with retroviruses.<sup>274</sup> Patent protection was extended until the end of 2008 in the U.S. and until 2011 in most European countries. BMS markets d4T under a marketing and distribution licence from Yale University. Patents should have expired in most other countries at this point.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

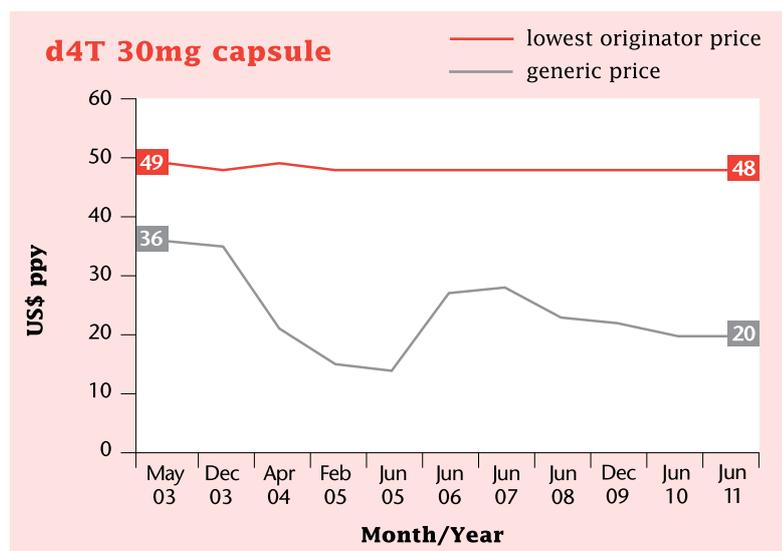
The price in brackets corresponds to the price of one capsule/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

	Daily dose	BMS		Aspen	Aurobindo (CF)	Cipla	Hetero	Ranbaxy	Strides
		Category 1 countries	Category 2 countries						
Who can access this price?		See annex 2 & annex 7		See annex 2					
d4T 1mg/ml powder for oral solution	20 ml	<b>58 (0.008/ml)</b>	No discounted price		<b>58 (0.008/ml)</b>	<b>51 (0.007/ml)</b>			
d4T 15mg capsule	-	<b>(0.083)</b>	<b>(0.118)</b>	(0.027)	<b>(0.024)</b>		<b>(0.025)</b>		
d4T 20mg capsule	-	<b>(0.094)</b>	<b>(0.118)</b>	<b>(0.031)</b>	<b>(0.025)</b>		<b>(0.028)</b>		
d4T 30mg capsule	2	<b>48 (0.066)</b>	<b>86 (0.118)</b>		<b>20 (0.027)</b>		<b>21 (0.029)</b>	<b>24 (0.033)</b>	<b>22 (0.030)</b>

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

Continued overleaf ❖

## Stavudine (d4T) continued



### Evolution of the lowest price quoted for developing countries since 2003:

As of May 2011, seven generic sources of d4T 30mg capsule were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

The first generic source of d4T 30mg capsule was quality-assured by WHO prequalification in June 2005 – the generic price in the graph above corresponds to the lowest generic price until that date, and to the lowest quality-assured generic price from that date on.

## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine- (d4T) based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir- (TDF) based first-line regimens.

For many years, the regimen containing d4T has played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and most importantly its low cost. d4T remains a widely used ARV in first-line regimens.

During the review of the marketing authorisation of this medicine in February 2011, the European Medicines Agency (EMA) decided to severely restrict its use in both adults and children, recommending that in view of its long-term toxicities, d4T be used for as short a time as possible and only when no appropriate alternatives<sup>8</sup> exist.

In some African countries including Ethiopia, Ghana, Kenya, Nigeria, Tanzania and Uganda, Bristol-Myers Squibb (BMS) discontinued all

commercial activities by the end of 2009, including deregistration of all BMS products.<sup>26</sup> BMS also discontinued the marketing of d4T products in South Africa in December 2010.

### Patents

Yale University did not apply for patents in most developing countries except for South Africa. Generic manufacturers from countries with manufacturing capacity, such as Brazil, China, India or Thailand could therefore legally manufacture and export affordable generic versions of d4T.

In South Africa, where BMS marketed d4T under an exclusive licence from Yale, the drug was 34 times more expensive than generic versions available in other countries. This prompted controversy in March 2001, particularly as the medicine had been developed with public funds. After pressure from researchers, students, and access advocates, Yale renegotiated its licence with BMS to allow the importation of more affordable generic versions of d4T to South Africa.<sup>273</sup>

### Paediatrics

d4T is approved for use in children.<sup>277</sup> In its 2010 guidelines for antiretroviral

therapy for HIV in infants and children, WHO recommends d4T as one of the possible NRTIs to be given with 3TC and either an NNRTI or a PI in the first-line.<sup>22</sup>

Because of the long-term risks of toxicity, particularly lipoatrophy in children treated with d4T-containing regimens, the use of AZT is preferred. Toxicity risks are also associated with AZT, with possible anaemia developing over the first few months of therapy, but the drug remains much better tolerated than d4T.<sup>22</sup> WHO guidelines recommend a preferential order of NRTIs to be used in first-line regimens, with AZT preferred over ABC, and ABC preferred over d4T.

The paediatric formulation of d4T is not adapted for resource-limited settings as it is supplied as a powder that requires reconstitution with clean, safe water, and once reconstituted, must be refrigerated.

Generic manufacturers have however been developing both double and triple fixed-dose combinations including d4T. As of May 2011, four d4T-containing FDCs for paediatric use were quality-assured by either US FDA or WHO prequalification.

# TENOFOVIR DISOPROXIL FUMARATE (TDF)

## GENERAL INFORMATION

- Therapeutic class: Nucleotide reverse transcriptase inhibitor (NtRTI).
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- World sales of originator product: 2010: US\$ 732 million; 2009: \$667 million; 2008: \$621 million; 2007: \$613 million; 2006: \$689 million; 2005: \$778 million; 2004: \$783 million.<sup>128, 129, 130, 131, 132, 278, 279</sup>
- Patents: The basic patent on tenofovir was applied for by the Academy of Sciences of the former Czechoslovakia in 1986. It has now expired in most countries.<sup>280</sup> Gilead subsequently applied for additional patents related to tenofovir disoproxil in 1997<sup>281</sup> and to the fumarate salt of tenofovir disoproxil in 1998.<sup>282</sup> These are due to expire in 2017 and 2018, respectively. In addition, Gilead and BMS have applied for patents on fixed-dose combinations of TDF/FTC and TDF/FTC/EFV which will not expire before 2024 and 2026 respectively,<sup>120, 121</sup> in countries where granted.
- WHO guidelines: Indicated for first- and second-line for adults, adolescents and children.<sup>6, 22</sup>
- Originator company and product brand name: Gilead, Viread.
- First approval by U.S. Food and Drug Administration (FDA): October 2001.<sup>23</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

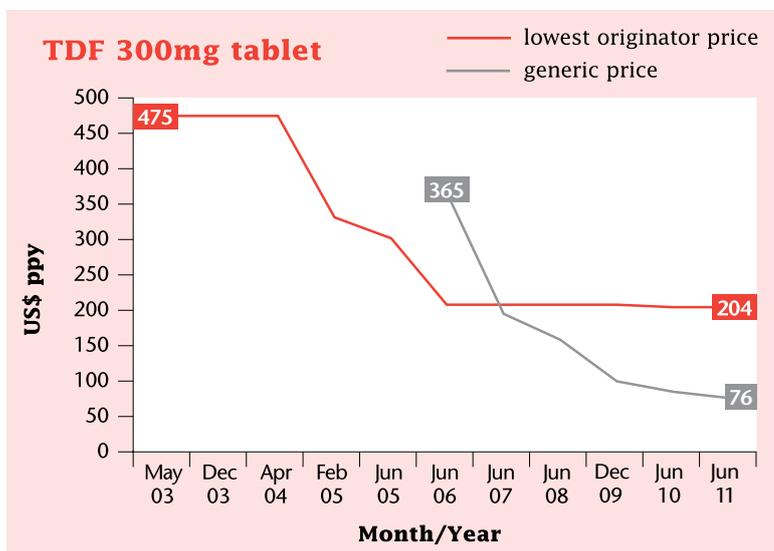
	Daily dose	Gilead		Aspen	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy (CF)	Strides
		Category 1 countries	Category 2 countries							
Who can access this price?		See annex 2 & annex 9			See annex 2					
TDF 300mg tablet	1	<b>204 (0.559)</b>	<b>360 (0.986)</b>	87 (0.237)	<b>88 (0.242)</b>	<b>83 (0.227)</b>	<b>103 (0.283)</b>	<b>76 (0.208)</b>	<b>97 (0.267)</b>	79 (0.217)

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest price quoted for developing countries since 2003:

As of May 2011, five generic sources of TDF 300mg tablet were quality-assured by US FDA and WHO prequalification. The one with the lowest price is shown here.

Since 2003, the originator price has decreased by 57%, while generic prices have dropped by 79%.



Continued overleaf

## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine- (d4T) based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir- (TDF) based first-line regimens.

For many years, the regimen containing d4T has played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and most importantly its low cost. d4T remains a widely used ARV in first-line regimens.

It is time for countries to invest in a more robust, TDF-containing first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which is one pill, once a day or TDF/3TC + NVP (available in co-pack). While the price today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition and the economies of scale needed to further decrease prices.<sup>7</sup>

TDF is also used in second-line treatment as the NRTI backbone – in combination with either lamivudine (3TC) or emtricitabine (FTC), to which a boosted protease inhibitor (PI) should be added – if d4T or AZT have been used in first-line treatment.

TDF is also active against the hepatitis B virus (HBV) and therefore plays an important role in co-infected patients. The latest WHO 2010 guidelines recommend using TDF with either FTC- or 3TC-containing antiretroviral

regimens in all HIV/HBV co-infected individuals needing treatment.<sup>7</sup>

### Patents

Gilead has applied for patents related to TDF in many developing countries, including Brazil, India and China.

Thanks to generic production that started in India in 2005 and to the patent oppositions filed by civil society groups in 2006<sup>283</sup> and 2007<sup>284</sup> to safeguard production, the price of TDF fell dramatically between 2005 and 2010. In a major victory for access to medicines, the Indian patent office rejected in September 2009 several patent applications, relating to the pro-drug,<sup>285</sup> the fumarate form<sup>286</sup> and the intermediate,<sup>287</sup> and the use of TDF in combination with FTC and EFV. The patents were rejected on the grounds that they lack an inventive step – they do not meet the requirement of enhanced efficacy stipulated under Section 3(d) of India's patent law.<sup>285, 286, 287</sup> Further, combinations of known molecules are not patentable under Indian patent law.<sup>288</sup>

Nevertheless, divisional applications have already been filed by Gilead for key applications covering pro-drug<sup>289</sup> and fumarate salt<sup>290</sup> and the combinations of TDF with FTC, EFV and LPV/r.<sup>290, 291</sup> These warrant additional pre-grant oppositions.

In 2006, while the oppositions by members of Indian and Brazilian civil society to the patent applications were still pending, Gilead signed voluntary licensing (VL) agreements with key generic manufacturers in India and one in South Africa. One generic manufacturer – Cipla – did not accept the VL and instead opted to file patent oppositions to protect the manufacture and availability of

its generic TDF – both domestically and for export.

Under the terms of the VL, Gilead and participating Indian manufacturers have divided up developing country markets for TDF and TDF-based fixed-dose combinations, whereby the generic manufacturers like Matrix could only export to a limited pre-defined list of countries, against the payment of a 5% royalty.<sup>139</sup> The VLs also include geographic market limitations. Participating manufacturers are unable to supply countries such as Brazil, Sri Lanka and China, leaving these countries unable to benefit from competitive prices or to improve access. Following negotiations with Gilead, Brazil is today paying \$715 ppy for TDF. This is over nine times the best available generic price.<sup>76</sup>

In Brazil, civil society groups filed an opposition contesting Gilead's patent application for TDF in December 2006.<sup>292</sup> In April 2008, the government declared TDF as a medicine of public interest for priority examination purposes, and in September 2008, the Brazilian patent office published the patent rejection. However, in January 2010, Gilead launched a legal challenge against the patent office's decision to reject the patent. Gilead also requested a divisional patent, which was opposed by civil society groups,<sup>293</sup> and in another victory for access to medicines, rejected in May 2011.<sup>294</sup>

In February 2011, the Brazilian government announced the beginning of local production of TDF through a partnership between Brazilian public and private manufacturers.<sup>295</sup>

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⋮ *Continued from below left*

The access challenges Brazil experiences today will be faced by other developing countries in coming years, and Brazil's actions to improve the accessibility and affordability of TDF<sup>147</sup> and other newer medications will have wider implications for all developing countries. Price reductions achieved by Brazil will set a target price for other countries, especially for other middle- and lower middle-income countries.

The size of Brazil's cohort is also critical. With approximately 64,000 people taking TDF,<sup>147</sup> the country could stimulate an international generic market where prices are reduced through competition and economies of scale.

### **Paediatrics**

In March 2010, TDF was approved by US FDA for use in adolescents older than 12 years old and weighing more than 35kg.<sup>297</sup> 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. Having safety and efficacy data in paediatric populations would enable children to stay longer on the same treatment regimen, and would facilitate harmonisation with adult regimens, as TDF-based first-line

regimens are also the preferred option for adults.

In March 2009, US FDA granted TDF an Orphan Drug designation for treatment of paediatric HIV infections.<sup>298</sup> Gilead is now entitled to seven years of marketing exclusivity for the designated paediatric indication, tax credits for clinical research and can apply for grants to defray the cost of clinical trials.<sup>299</sup>



# TIPRANAVIR (TPV)

## GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).<sup>5</sup>
- WHO guidelines: Not currently included in WHO guidelines. TPV is indicated for combination treatment of HIV-1 infected adult patients who are treatment-experienced and infected with HIV-1 strains resistant to more than one protease inhibitor.<sup>300</sup>
- Originator company and product brand name: Boehringer Ingelheim (BI), Aptivus.
- First approval by U.S. Food and Drug Administration (FDA): June 2005.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Not included in the 17th edition.<sup>24</sup>
- World sales of originator product: There are no sales figures listed in the company's annual report.
- Patents: The basic patent was applied for by Upjohn in May 1995,<sup>301</sup> and is due to expire in 2015. In 1998, Pharmacia & Upjohn applied for additional patents related to pharmaceutical formulations suitable for the oral administration of TPV.<sup>302, 303</sup> In January 2000, BI acquired worldwide rights for TPV.

## PRICE INFORMATION

**Boehringer Ingelheim was invited to contribute a price for this publication and has communicated it does not offer a reduced price for developing countries.**

## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors (PI), to be taken in combination with two NRTIs. They are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r). As tipranavir (TPV) was not identified as one of the priority products, its use in the developing world will be limited.<sup>7</sup>

TPV, like all PIs (with the exception of nelfinavir (NFV)), requires boosting with RTV. Abbott's heat-stable ritonavir received marketing approval in the U.S. and Europe in early 2010. Registering this new formulation in developing countries will be crucial in order to allow the use of other PIs than lopinavir. A generic heat-stable RTV is now available and was WHO prequalified in late 2010.

One further limitation concerning TPV is that the capsules require refrigeration until dispensing.

Boehringer Ingelheim has communicated that TPV is available through its Compassionate Use Program and that the company is currently filing for registration in various countries.

### Patents

TPV patents have been filed widely in developing countries with generic production capacity, such as Brazil and China.<sup>38</sup>

In Brazil, where the patent applications are under review, the drug regulatory agency (ANVISA), which has to give 'prior consent' for any patent application related to a medicine, advised for the rejection of the basic patent application.<sup>304</sup> In early 2007, civil society expressed concerns over the delays to the registration procedure of TPV in Brazil – the medicine had been tested in Brazilian patients in 14 research centres since February 2004, but the drug was not actually registered in the country. After

considerable civil society pressure, the registration was eventually filed with ANVISA at the end of February 2008, almost three years after US FDA and EMA approvals. The intervention by Brazilian civil society was partly based in response to suspicions that Boehringer Ingelheim did not want to register the product in the country, unless they had the guarantee that the patent would be granted by the patent office.<sup>305, 306, 307</sup>

### Paediatrics

TPV is currently approved for use in children from two years of age and older.<sup>23</sup>

A paediatric oral solution exists. However, TPV must be given with a RTV booster, but the RTV solution currently available has a bitter aftertaste and contains 43% alcohol, and is thus not adapted for children, limiting the use of TPV in this population.

# ZIDOVUDINE (AZT or ZDV)

## GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- WHO guidelines: Indicated for first- and second-line for adults, adolescents and children.<sup>6,22</sup>
- Originator company and product brand name: GlaxoSmithKline (GSK), Zidovudine. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): March 1987.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- World sales of originator product: 2005: US\$ 84 million; 2004: \$80 million. After 2005, there are no sales figures for this product listed in the company's annual report.<sup>26,27</sup>
- Patents: AZT was first discovered in 1964 as an anti-cancer medicine. The U.S. National Institutes of Health funded the majority of the research that showed the drug's effectiveness as an antiretroviral. Glaxo Wellcome filed patents on AZT for the treatment of AIDS and brought the drug onto the market in 1987 as one of the most expensive ever sold. Patents have expired in most countries at this point.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

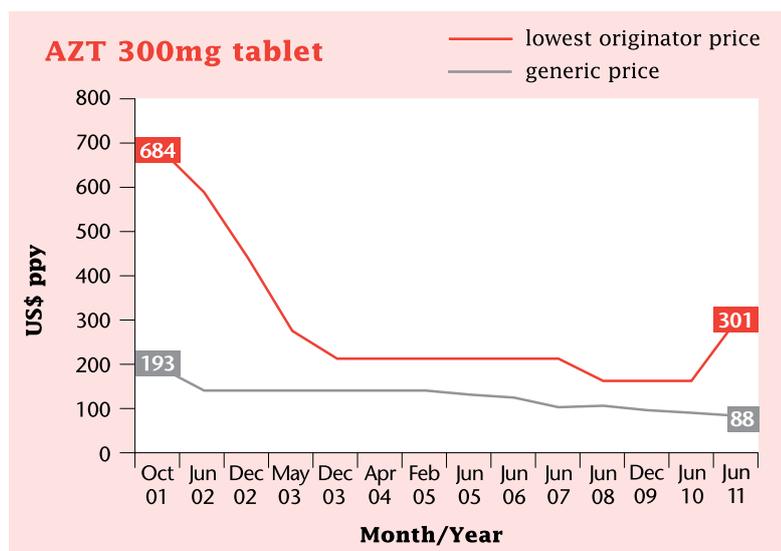
The price in brackets corresponds to the price of one tablet/capsule/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

	Daily dose	ViiV	Aspen	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Micro Labs (CF)	Ranbaxy
Who can access this price?		See annex 2							
AZT 10mg/ml oral solution	20ml	<b>380 (0.052/ml)</b>	88 (0.012/ml)	<b>66 (0.009/ml)</b>	<b>110 (0.015/ml)</b>	73 (0.010/ml)			
AZT 60mg tablet	4			<b>115 (0.079)</b>					
AZT 100mg capsule	-	<b>(0.185)</b>		<b>(0.048)</b>	<b>(0.055)</b>				
AZT 250mg tablet	-	<b>(0.301)</b>							
AZT 300mg tablet	2	<b>301 (0.412)</b>	<b>99 (0.136)</b>	<b>88 (0.121)</b>	<b>91 (0.125)</b>	<b>100 (0.137)</b>	<b>88 (0.121)</b>	<b>91 (0.125)</b>	<b>91 (0.125)</b>

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

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❖ Zidovudine (AZT or ZDV) continued



### Evolution of the lowest price quoted for developing countries since 2001:

As of May 2011, seven generic sources of AZT 300mg tablet were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

The originator price increased for the first time this year by 87% compared to 2010, while the generic price has steadily decreased by 54% since 2001.

## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine- (d4T) based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir- (TDF) based first-line regimens.

For many years, the regimen containing d4T has played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and most importantly its low cost. d4T remains a widely used ARV in first-line regimens.

AZT is also used in second-line treatment as the NRTI backbone – in combination with either lamivudine (3TC) or emtricitabine (FTC), to which a boosted protease inhibitor (PI) should be added – if d4T or AZT have been used in first-line treatment.

In 2011, ViiV clarified their pricing structure (see annex 2), confirming that their differential prices 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 those prices, and will have to negotiate prices on a case-by-case basis.

### Patents

Patents have expired in most countries at this point.

### Paediatrics

AZT is approved for use and is widely used in children.<sup>307</sup> In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends AZT as the preferred NRTI to be given with 3TC and either an NNRTI or a PI in the first-line. AZT can also be part of second-line regimens, depending on what has been used as a first-line.<sup>22</sup>

Because of the long-term risks of toxicity, particularly lipoatrophy in children treated with d4T-containing regimens, the use of AZT is preferred. Toxicity risks are also associated with AZT, with possible anaemia developing over the first few months of therapy, but the drug remains much better tolerated than d4T.<sup>22</sup> WHO guidelines recommend a preferential order of NRTIs to be used in first-line regimens, with AZT preferred over ABC, and ABC preferred over d4T.

As of April 2011, there is one generic version of AZT 60mg quality-assured by US FDA.

Generic manufacturers have also been developing both double and triple paediatric fixed-dose combinations including AZT. As of May 2011, four paediatric FDCs containing AZT were quality-assured by either US FDA or WHO prequalification.

# ABACAVIR/ LAMIVUDINE (ABC/3TC)

## GENERAL INFORMATION

- Therapeutic class: Two NRTI in a double fixed-dose combination.
- WHO guidelines: Indicated for first- and second-line for children and as part of triple NRTI drugs under specific conditions in adults, adolescents and children.<sup>6,22</sup>
- Originator company and product brand name: GlaxoSmithKline (GSK), Kivexa (EU), Epzicom (U.S.). In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): August 2004.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Individual medicines included in the 17th edition. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.<sup>24</sup>
- World sales of originator product: 2010: US\$ 899 million; 2009: \$834 million; 2008: \$721 million; 2007: \$641 million; 2006: \$475 million; 2005: \$233 million.<sup>163, 25, 27, 28, 29, 30</sup>
- Patents: Most patents on abacavir (ABC) or lamivudine (3TC) also affect this combination. In addition, GSK applied for patents more specifically related to the combination.<sup>308</sup> The patent expiry dates related to this combination are 2016 in the U.S. and 2019 in EU.<sup>30</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

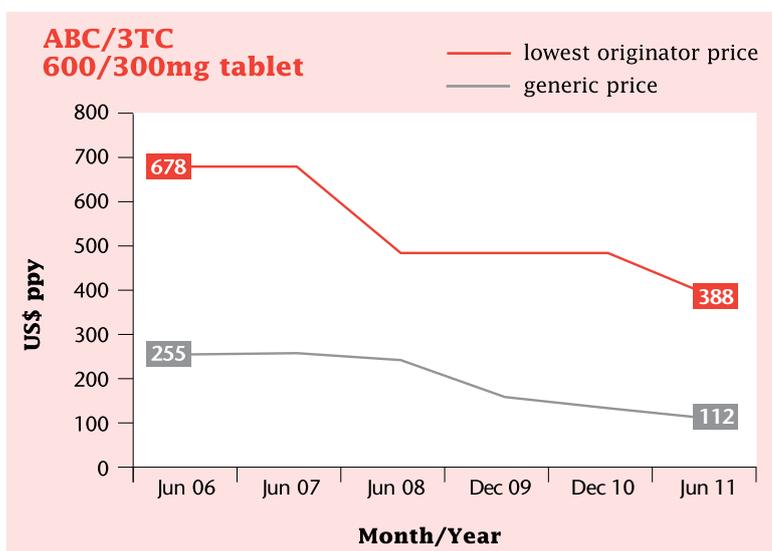
	Daily dose	ViiV	Aurobindo (CF)	Matrix (CF)
Who can access this price?		See annex 2		
ABC/3TC 60/30mg tablet	4		<b>175 (0.120)</b>	<b>292 (0.200)</b>
ABC/3TC 600/300mg tablet	1	388 (1.064)	<b>112 (0.308)</b>	<b>280 (0.767)</b>

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest price quoted for developing countries since 2006:

As of May 2011, two generic source of ABC/3TC 600/300mg tablet were quality-assured by US FDA or WHO prequalification. The lowest price is shown here.

Since 2006, the originator price has decreased by 43%, while generic prices have dropped by 56%.



Continued overleaf

## SPOTLIGHT ON ACCESS ISSUES

This combination is likely to fall out of favour since the latest 2010 WHO guidelines for adults and adolescents recommend treatment consisting of either AZT or TDF. It remains an important combination for the treatment of paediatric HIV, however.

In 2011, ViiV clarified their pricing structure (see annex 2), confirming that their differential prices 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 those prices, and will have to negotiate prices on a case-by-case basis.

In February 2011, Shionogi-ViiV Healthcare announced the start of a phase III trial for a new fixed-dose combination including ABC, lamivudine (3TC)<sup>36</sup> and a new integrase inhibitor S/GSK1349572 (an investigational drug known as dolutegravir, now in phase III clinical development).<sup>37</sup>

### Patents

GlaxoSmithKline could not apply for basic patents related to ABC or 3TC in some developing countries such as India that did not grant patents on pharmaceutical products at

the time. This allowed Indian drug manufacturers to develop generic versions of each medicine, and of the combination of the two.

However, GSK widely applied for patents in other developing countries where possible.

### Paediatrics

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends ABC/3TC as one of the possible combinations to be given with either an NNRTI or a PI in the first-line. ABC/3TC can also be part of second-line regimens, depending on what has been used as a first-line. WHO guidelines recommend a preferential order of NRTIs to be used in first-line regimens, with AZT preferred over ABC, and ABC preferred over d4T.<sup>22</sup>

ABC will nevertheless continue to be an important drug for HIV/TB co-infected young children, not least because children have limited treatment options – there are interactions between TB drugs and nevirapine (NVP), and the dosage data on efavirenz (EFV) for children under three is lacking.

However, a recent survey regarding paediatric second-line carried out by the TREAT Asia Paediatric HIV

Observational Database (TApHOD) found that ABC was more difficult to access in Asia and that its relatively high cost could act as a deterrent to wider use.<sup>41</sup> This applies particularly in countries where ABC is patented and where the generic ABC/3TC 60/30mg tablet is not available.

For children who need this combination, two generic sources of ABC/3TC 60/30mg are quality-assured by either US FDA or WHO prequalification. However, in countries where ABC is patented, the generic tablet is not available, and ViiV does not produce a fixed-dose combination of these drugs for children – even though the FDCs exist for adults.

The Paediatric Antiretroviral Working Group of WHO considers the development of a scored adult fixed-dose combination of ABC/3TC 300/150mg tablet, for use in children weighing over 25kg, to be a high priority.<sup>22</sup>

The Working Group also considers the development of a triple fixed-dose combination of ABC/3TC/NVP 60/30/50mg tablet to be a high priority.<sup>22</sup> This formulation does not exist yet although it is needed to simplify first-line treatment.

# LAMIVUDINE/ STAVUDINE (3TC/d4T)

## GENERAL INFORMATION

- Therapeutic class: Two NRTI in a double fixed-dose combination.
- WHO guidelines: Indicated for first-line in children WHO 2009 guidelines also recommended to move away from d4T first-line in adults and adolescents.<sup>6,22</sup> WHO updated the 2006 guidelines to recommend a reduction in dose of d4T 40mg to d4T 30mg for all weight categories of patients.<sup>22</sup>
- Originator company and product brand name: No originator product exists.
- First approval by U.S. Food and Drug Administration (FDA): not applicable.
- WHO Model List of Essential Medicines (EML): Individual medicines included in the 17th edition. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.<sup>24</sup>
- Patents: Individual patents on lamivudine (3TC) or stavudine (d4T) also affect this combination.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

	Daily dose	Cipla (CF)	Hetero (CF)	Matrix	Ranbaxy (CF)	Strides
Who can access this price?		See annex 2				
3TC/d4T 30/6mg dispersible tablet	4	<b>47</b> <b>(0.032)</b>				
3TC/d4T 60/12mg dispersible tablet	2	<b>40</b> <b>(0.055)</b>				
3TC/d4T 150/30mg tablet	2	<b>42</b> <b>(0.058)</b>	<b>46</b> <b>(0.063)</b>	<b>39</b> <b>(0.054)</b>	<b>42</b> <b>(0.058)</b>	<b>41</b> <b>(0.056)</b>

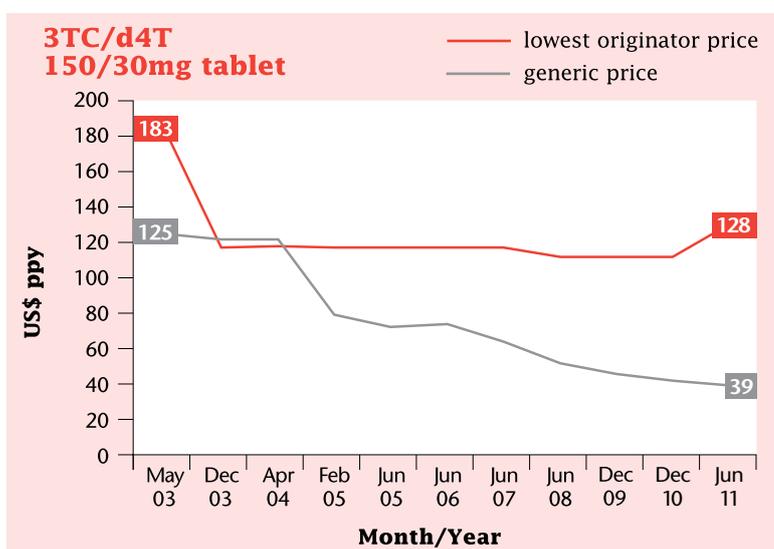
(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest price quoted for developing countries since 2003:

As of May 2011, seven generic sources of 3TC/d4T 150/30mg tablet were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

As there is no originator fixed-dose combination or co-pack, the price shown for the originator product is the sum of the two individual originator products.

Since 2003, the sum of the originator prices has decreased by 30%, while generic prices have dropped by 69%.



Continued overleaf

## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out d4T-based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir-based (TDF) first-line regimens.<sup>7</sup>

For many years, the stavudine- (d4T) containing regimen played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and, most importantly, its low cost. d4T remains a widely used ARV in first-line regimens.

During the review of the marketing authorisation of this medicine in February 2011, the European Medicines Agency (EMA) decided to severely restrict its use in both adults and children, recommending that in view of its long-term toxicities, d4T be used for as short a time as possible and only when no appropriate alternatives<sup>8</sup> exist.

It is time for countries to invest in a more robust, TDF-containing first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which are both one pill, once a day or TDF/3TC + NVP

(available in co-pack). While the price today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition and the economies of scale needed to further decrease prices.<sup>7</sup>

We can therefore expect to see a decrease in the use of this formulation in the future.

### Patents

Generic companies in certain developing countries were able to develop these fixed-dose combinations because patents on the individual products did not exist.

The fixed-dose combination is not available in developed countries or in countries such as China, however, where one or both medicines are under patent.

### Paediatrics

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends 3TC/d4T as one of the possible combinations to be given with either an NNRTI or a PI in the first-line.<sup>22</sup>

3TC/d4T, when used with NVP, is part of one of the two most commonly used first-line regimens for children today (the other being

AZT/3TC/NVP). With both of these regimens, there is a need to start NVP at a lower dose for the first two weeks to minimise the side effects. Quality-assured double fixed-dose combinations are therefore of great value in allowing children to be safely and accurately dosed while starting treatment. In their absence, the alternative is to use two different syrups, which can be difficult to administer.

Because of the long-term risks of toxicity, particularly lipoatrophy in children treated with d4T-containing regimens, the use of AZT is preferred. Toxicity risks are also associated with AZT, with possible anaemia developing over the first few months of therapy, but the drug remains much better tolerated than d4T.<sup>22</sup> WHO guidelines recommend a preferential order of NRTIs to be used in first-line regimens, with AZT preferred over ABC, and ABC preferred over d4T.

As of May 2011, two generic dispersible formulations were quality-assured by either US FDA or WHO prequalification.

# LAMIVUDINE/STAVUDINE/ NEVIRAPINE (3TC/d4T/NVP)

## GENERAL INFORMATION

- Therapeutic class: Two NRTI and one NNRTI in a triple fixed-dose combination.
- WHO guidelines: Indicated for first-line for children. WHO 2009 guidelines also recommended to move away from d4T first-line in adults and adolescents.<sup>6,22</sup> WHO updated the 2006 guidelines to recommend a reduction in dose of d4T 40mg to d4T 30mg for all weight categories of patients.<sup>22</sup>
- Originator company and product brand name: No originator product exists.
- First approval by U.S. Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Included in the 17th edition – only the d4T 30mg presentation.<sup>24</sup> The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.<sup>24</sup>
- Patents: Individual patents on lamivudine (3TC), stavudine (d4T) or nevirapine (NVP) also affect this combination. Cipla first developed the FDC and applied for patents in several African countries.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

	Daily dose	Cipla (CF)	Hetero (CF)	Ranbaxy (CF)	Strides	Varichem
Who can access this price?		See annex 2				
3TC/d4T/NVP 30/6/50mg dispersible tablet	4	<b>55 (0.038)</b>				
3TC/d4T/NVP 60/12/100mg dispersible tablet	2	<b>53 (0.072)</b>				
3TC/d4T/NVP 150/30/200mg tablet	2	<b>64 (0.088)</b>	<b>67 (0.092)</b>	<b>70 (0.096)</b>	<b>66 (0.090)</b>	<b>61 (0.083)</b>

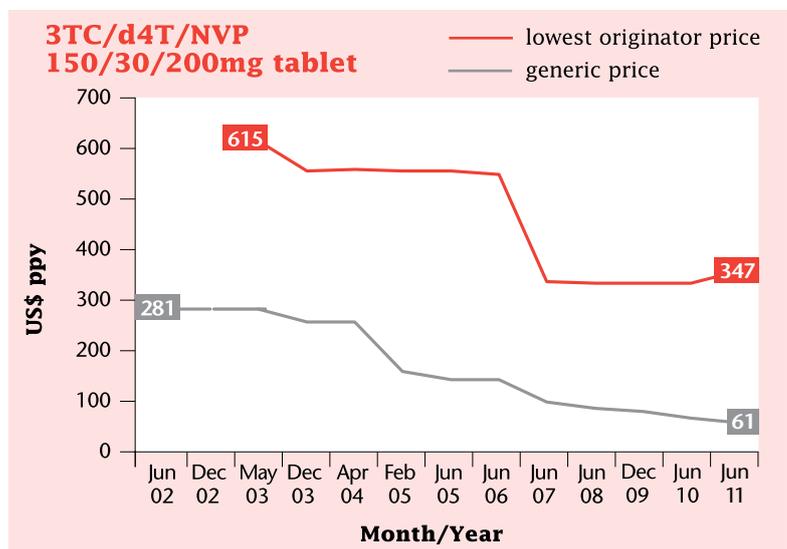
(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest price quoted for developing countries since 2002:

As of May 2011, ten generic sources of 3TC/d4T/NVP 150/30/200mg tablet were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

As there is no originator fixed-dose combination or co-pack, the price shown for the originator product is the sum of the three individual originator products.

Since 2002, the sum of the originator prices has decreased by 44%, while generic prices have dropped by 78%.



Continued overleaf

## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out d4T-based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir-based (TDF) first-line regimens.<sup>7</sup>

For many years, the stavudine- (d4T) containing regimen played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and, most importantly, its low cost. d4T remains a widely used ARV in first-line regimens.

During the review of the marketing authorisation of this medicine in February 2011, the European Medicines Agency (EMA) decided to severely restrict its use in both adults and children, recommending that in view of its long-term toxicities, d4T be used for as short a time as possible and only when no appropriate alternatives<sup>8</sup> exist.

It is time for countries to invest in a more robust, TDF-containing first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which are both one pill, once a day or TDF/3TC + NVP (available in co-pack). While the price today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition and the economies of scale needed to further decrease prices.<sup>7</sup>

We can therefore expect to see a decrease in the use of this formulation in the future.

### Patents

Cipla was able to develop this combination because none of the individual components were patented in India. Many generic manufacturers have followed suit in other developing countries, such as Thailand, where the medicines were not patented.

Extensive competition from numerous generic manufacturers has made this combination the most affordable triple ARV combination treatment to date.

### Paediatrics

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends 3TC/d4T as one of the possible combinations to be given with either an NNRTI or a PI in the first-line.<sup>22</sup>

Because of the long-term risks of toxicity, particularly lipoatrophy in children treated with d4T-containing regimens, the use of AZT is preferred. Toxicity risks are also associated with AZT, with possible anaemia developing over the first few months of therapy, but the drug remains much better tolerated than d4T.<sup>22</sup> WHO guidelines recommend a preferential order of NRTIs to be used in first-line regimens, with AZT preferred over ABC, and ABC preferred over d4T.

However, together with AZT/3TC/NVP, 3TC/d4T/NVP is one of the two most commonly used first-line regimens for children today. With both of these regimens, there is a need to start NVP at a lower dose for the first two weeks to minimise the side effects, and therefore the 3TC/d4T double fixed-dose combination is of great value in allowing children to be safely and accurately dosed while starting treatment. In their absence, the alternative is to use two different syrups, which can be difficult to administer.

The Paediatric Working Group at WHO has released clear guidance on the ideal strength of each of the individual ARVs in these fixed-dose combinations.

As of May 2011, two dispersible formulations were quality-assured by either US FDA or WHO prequalification.<sup>43</sup>

HIV/TB co-infected young children cannot be given NVP because of interactions between NVP and TB drugs. As there is still no established dosing of EFV, the standard alternative to NVP, for children less than three years of age, there is an urgent need to establish the dosing of EFV for this age group.

# LAMIVUDINE/STAVUDINE + EFAVIRENZ (3TC/d4T + EFV)

## GENERAL INFORMATION

- Therapeutic class: Two NRTI (in a fixed-dose combination) + one NNRTI in a co-pack.
- WHO guidelines: Indicated for first-line for children. WHO 2009 guidelines also recommended to move away from d4T first-line in adults and adolescents.<sup>6,22</sup> WHO updated the 2006 guidelines to recommend a reduction in dose of d4T 40mg to d4T 30mg for all weight categories of patients.<sup>272</sup>
- Originator company and product brand name: No originator product exists.
- First approval by U.S. Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Individual medicines included in the 17th edition. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.<sup>24</sup>
- Patents: Individual patents on lamivudine (3TC), stavudine (d4T) or efavirenz (EFV) also affect this combination.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one kit of 3 tablets. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

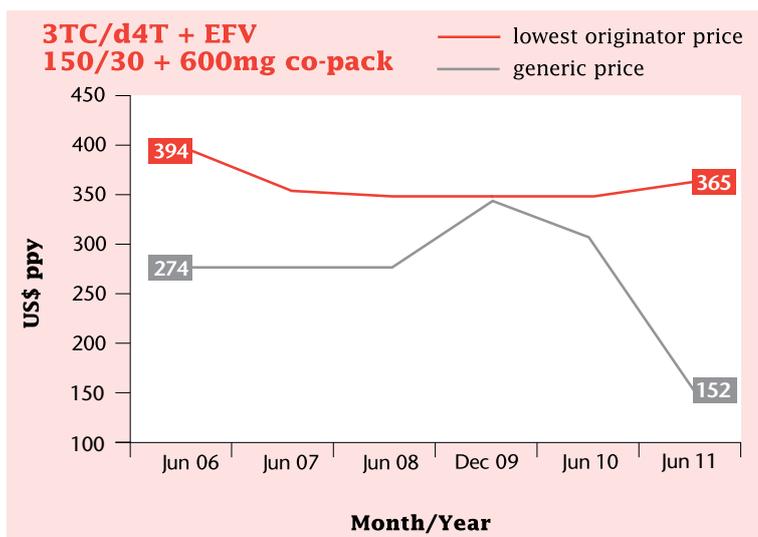
	Daily dose	Ranbaxy	Strides
Who can access this price?		See annex 2	
3TC/d4T + EFV 150/30 + 600mg tablets (co-pack)	1 kit (3 tablets)	<b>152 (0.417)</b>	106 (0.290)

### Evolution of the lowest price quoted for developing countries since 2006:

As of May 2011, one generic source of 3TC/d4T + EFV 150/30 + 600mg co-pack was quality-assured by US FDA or WHO prequalification. Its price is shown here.

As there is no originator co-pack, the price shown for the originator product is the sum of the three individual originator products.

Since 2006, the sum of the originator prices has decreased by 7%, while generic prices have dropped by 45%.



Continued overleaf ❖

## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out d4T-based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir-based (TDF) first-line regimens.<sup>7</sup>

For many years, the stavudine- (d4T) containing regimen played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and, most importantly, its low cost. d4T remains a widely used ARV in first-line regimens.

During the review of the marketing authorisation of this medicine in February 2011, the European Medicines Agency (EMA) decided to severely restrict its use in both adults and children, recommending that in view of its long-term toxicities, d4T be used for as short a time as possible and only when no appropriate alternatives<sup>8</sup> exist.

It is time for countries to invest in a more robust, TDF-containing first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which are both one pill, once a day or TDF/3TC + NVP (available in co-pack). While the price today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition and the economies of scale needed to further decrease prices.<sup>7</sup>

We can therefore expect to see a decrease in the use of this formulation in the future.

### Patents

Generic companies in certain developing countries were able to develop this co-blister because patents on the individual components contained in the combination did not exist.

This product is not available in developed countries or in China because of various patents on 3TC, d4T and/or EFV.

### Paediatrics

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends 3TC/d4T as one of the possible combinations to be given with either an NNRTI or a PI in the first-line.<sup>22</sup>

Because of the long-term risks of toxicity, particularly lipoatrophy in children treated with d4T-containing regimens, the use of AZT is preferred. Toxicity risks are also associated with AZT, with possible anaemia developing over the first few months of therapy, but the drug remains much better tolerated than d4T.<sup>22</sup> WHO guidelines recommend a preferential order of NRTIs to be used in first-line regimens, with AZT preferred over ABC, and ABC preferred over d4T.

As there is still no established dosing of EFV for children less than three years of age, there is an urgent need to establish the dosing of EFV for this age group for children with HIV/TB co-infection.

In the absence of such data, treatment options for children remain limited, particularly for HIV/TB co-infected young children who cannot be given NVP because of interactions between NVP and TB drugs.

Currently a co-pack of d4T/3TC + EFV for children does not exist.

# TENOFOVIR DISOPROXIL FUMARATE/EMTRICITABINE (TDF/FTC)

## GENERAL INFORMATION

- Therapeutic class: One NtRTI and one NRTI in a double fixed-dose combination.
- WHO guidelines: Indicated for first-line and second-line for adults and adolescents.<sup>6</sup>
- Originator company and product brand name: Gilead, Truvada.
- First approval by U.S. Food and Drug Administration (FDA): August 2004.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Included in the 17th edition. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.<sup>24</sup>
- World sales of originator product: 2010: US\$ 2.65 billion; 2009: \$2.49 billion; 2008: \$2.11 billion; 2007: \$1.59 billion; 2006: \$1.19 billion; 2005: \$568 million; 2004: \$68 million.<sup>128, 129, 132</sup>
- Patents: Most patents related to tenofovir (TDF) or to emtricitabine (FTC) also affect this combination. In addition, Gilead applied for patents specifically related to this combination in 2004, which are due to expire in 2024.<sup>120</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

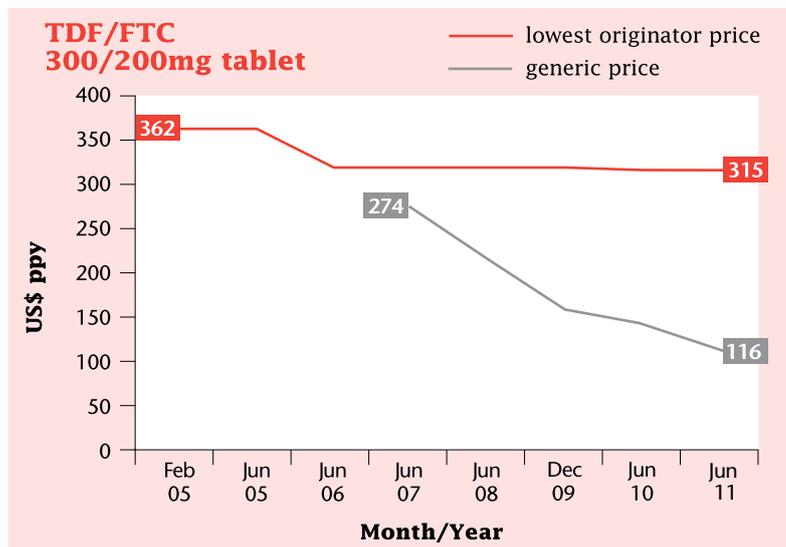
	Daily dose	Gilead		Aurobindo (CF)	Cipla (CF)	Hetero	Matrix (CF)
		Category 1 countries	Category 2 countries				
Who can access this price?		See annex 2 & annex 9		See annex 2			
TDF/FTC 300/200mg tablet	1	<b>315 (0.863)</b>	<b>540 (1.479)</b>	<b>140 (0.383)</b>	134 (0.367)	164 (0.450)	<b>116 (0.317)</b>

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest price quoted for developing countries since 2005:

As of May 2011, two generic sources of TDF/FTC 300/200mg tablet were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

Since 2005, the originator price has decreased by 13%, while generic prices have dropped by 58% since 2007.



Continued overleaf

## SPOTLIGHT ON ACCESS ISSUES

This combination is likely to be widely used in developing countries as a backbone in first- and second-line regimens.

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine- (d4T) based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir- (TDF) based first-line regimens.

For many years, the regimen containing d4T played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and most importantly its low cost. d4T remains a widely used ARV in first-line regimens.

It is time for countries to invest in a more robust, TDF-containing first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which are both one pill, once a day or TDF/3TC + NVP (available in co-pack). While the price today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition and the economies of scale needed to further decrease prices.<sup>7</sup>

TDF is also recommended for second-line treatment if d4T or AZT have been used in first-line.

TDF should then be used as the NRTI backbone, in combination with either lamivudine (3TC) or emtricitabine (FTC), to which a boosted protease inhibitor (PI) should be added.

TDF is also active against hepatitis B Virus (HBV) and therefore plays an important role in co-infected patients. The latest WHO 2010 guidelines recommend using TDF with either FTC- or 3TC-containing antiretroviral regimens in all HIV/HBV co-infected individuals needing treatment.<sup>22</sup>

### Patents

This combination is produced by Indian generic companies because neither of the individual components is patented in India today. However, Gilead has applied for patents related to TDF, which if granted will affect the production of not only TDF but also of this combination.

For further details on the patent status of TDF in India and Brazil, the voluntary licences agreements signed by Gilead and generic companies, and the Brazilian initiative for local production, please refer to the tenofovir drug profile.

### Paediatrics

TDF is approved for adolescents from 12 years old and FTC is approved for use in children, and both medicines have the advantage of once-daily dosing.

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. Having safety and efficacy data in paediatric populations would enable children to stay longer on the same treatment regimen, and would facilitate harmonisation with adult regimens, as TDF-based first-line regimens are also the preferred option for adults.

However, no paediatric fixed-dose combination has been developed combining these two medicines. There is an urgent need to have this combination developed for HIV and hepatitis B co-infected paediatric patients, for whom no treatment options currently exist.

# TENOFOVIR DISOPROXIL FUMARATE/EMTRICITABINE/EFVIRENZ (TDF/FTC/EFV)

## GENERAL INFORMATION

- Therapeutic class: One NtRTI + one NRTI + one NNRTI in a triple fixed-dose combination.
- WHO guidelines: Indicated for first-line for adults and adolescents.<sup>6</sup>
- Originator companies and product brand name: Gilead/Bristol-Myers Squibb/Merck, Atripla.
- First approval by U.S. Food and Drug Administration (FDA): July 2006.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Included in the 17th edition. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.<sup>24</sup>
- World sales of originator product: 2010: US\$ 2.927 billion; 2009: \$2.382 billion; 2008: \$1.572 billion; 2007: \$903 million; 2006: \$164 million (the product entered the market in the third quarter of the year).<sup>128, 132</sup>
- Patents: Most patents related to tenofovir (TDF), emtricitabine (FTC), TDF/FTC or to efavirenz (EFV) also affect this combination. In addition, Gilead and BMS jointly applied for patents specifically related to this combination in 2006,<sup>121</sup> which would last until 2026. Gilead pays royalties to BMS (and consequently Merck) for the EFV portion, originally owned by Dupont Merck, which was subsequently acquired by BMS.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

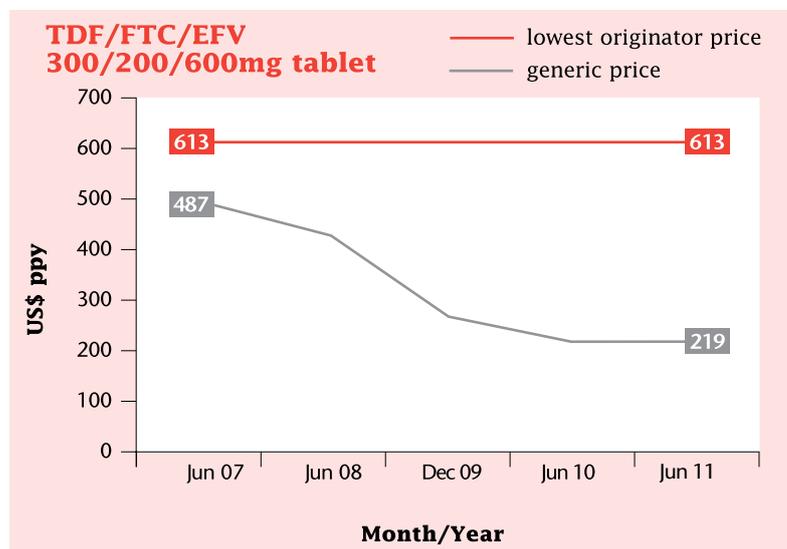
	Daily dose	BMS / Gilead / Merck		Cipla	Hetero	Matrix (CF)
		Category 1 countries	Category 2 countries			
Who can access this price?		See annex 2 & annex 10		See annex 2		
TDF/FTC/EFV 300/200/600mg tablet	1	<b>613 (1.680)</b>	<b>1033 (2.830)</b>	231 (0.633)	243 (0.667)	<b>219 (0.600)</b>

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest price quoted for developing countries since 2007:

As of May 2011, one generic source of TDF/FTC/EFV 300/200/600mg tablet was quality-assured by US FDA or WHO prequalification. Its price is shown here.

Since 2007, the originator price has remained stable, while generic prices have dropped by 55%.



Continued overleaf ❖

## SPOTLIGHT ON ACCESS ISSUES

This is a one-pill-a-day fixed-dose combination, which makes it well-adapted to resource-poor settings, although TDF/3TC/EFV is more affordable.

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine- (d4T) based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir- (TDF) based first-line regimens.

For many years, the regimen containing d4T played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and most importantly its low cost. d4T remains a widely used ARV in first-line regimens.

It is time for countries to invest in a more robust, TDF-containing first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which are both one pill, once a day or TDF/3TC + NVP (available in co-pack). While the price today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition and the economies of scale needed to further decrease prices.<sup>7</sup>

In addition, efavirenz (EFV) is the preferred NNRTI for use in patients starting ART while on tuberculosis treatment.

### Patents

This combination is produced by Indian generic companies because none of the individual components is patented in India today. However, Gilead<sup>309</sup> and BMS<sup>310</sup> have applied for patents related to TDF, including the one specifically related to this combination.<sup>311</sup> If these patents are granted in India, generic competition for this product may be affected.

For further details on the patent status of TDF in India and Brazil, the voluntary licences agreements signed by Gilead and generic companies, and the Brazilian initiative for local production, please refer to the tenofovir drug profile.

### Paediatrics

TDF is approved for adolescents from 12 years old, FTC is approved for use in children, and EFV is approved for use in children above three years old. All three medicines have the advantage of once-daily dosing.

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. Having safety and efficacy data in paediatric populations would enable children to stay longer on the same treatment regimen, and would facilitate harmonisation with adult regimens, as TDF-based first-line regimens are also the preferred option for adults.

However, no paediatric fixed-dose combination has been developed with TDF, FTC and EFV.

There is an urgent need to have this combination developed for HIV and hepatitis B co-infected paediatric patients, for whom no treatment options currently exist, as well as for HIV/TB co-infected young children who cannot be given NVP because of interactions between NVP and TB drugs.

As there is still no established dosing of EFV for children less than three years of age, there is an urgent need to establish the dosing of EFV for this age group for children with HIV/TB co-infection.

# TENOFOVIR DISOPROXIL FUMARATE/LAMIVUDINE (TDF/3TC)

## GENERAL INFORMATION

- Therapeutic class: One NtRTI and one NRTI in a double fixed-dose combination.
- WHO guidelines: Indicated for first- and second-line for adults and adolescents.<sup>6</sup>
- Originator company and product brand name: No originator product exists.
- First approval by U.S. Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Individual medicines included in the 17th edition. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.<sup>24</sup>
- Patents: Most patents related to tenofovir (TDF) or to lamivudine (3TC) also affect this combination. In addition, other patents may have been applied for, more specifically related to the use of these medicines in combination, or to this specific FDC, such as by Cipla.<sup>312</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

	Daily dose	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)
Who can access this price?		See annex 2			
TDF/3TC 300/300mg tablet	1	<b>116 (0.317)</b>	<b>103 (0.283)</b>	<b>116 (0.317)</b>	<b>91 (0.250)</b>

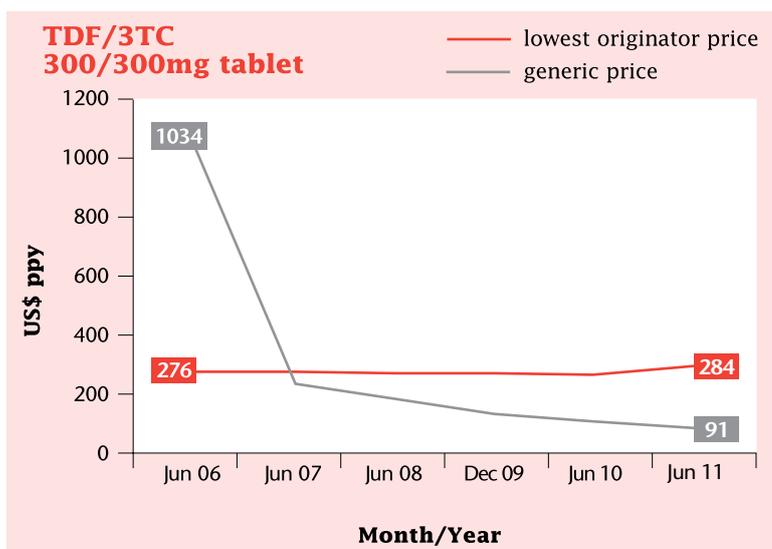
(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest quoted price for developing countries since 2006:

As of May 2011, four generic sources of TDF/3TC 300/300mg tablet were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

As there is no originator fixed-dose combination or co-pack, the price shown for the originator product is the sum of the two individual originator products.

Since 2006, the sum of the originator prices has increased by 3%, while generic prices have dropped by 91%. The most affordable generic product is 68% less expensive than the sum of the originator products.



Continued overleaf ❖

## SPOTLIGHT ON ACCESS ISSUES

This combination is likely to be widely used in developing countries as a backbone in first- and second-line regimens.

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine- (d4T) based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir- (TDF) based first-line regimens.

For many years, the regimen containing d4T played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and most importantly its low cost. d4T remains a widely used ARV in first-line regimens.

It is time for countries to invest in a more robust, TDF-containing first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which are both one pill, once a day or TDF/3TC + NVP (available in co-pack). While the price today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition and the economies of scale needed to further decrease prices.<sup>7</sup>

TDF is also recommended for second-line treatment if d4T or AZT have been used in first-line.

TDF should then be used as the NRTI backbone, in combination with either lamivudine (3TC) or emtricitabine (FTC), to which a boosted protease inhibitor (PI) should be added.

TDF is also active against hepatitis B Virus (HBV) and therefore plays an important role in co-infected patients. The latest WHO 2010 guidelines recommend using TDF with either FTC- or 3TC-containing antiretroviral regimens in all HIV/HBV co-infected individuals needing treatment.<sup>22</sup>

### Patents

This combination is produced by Indian generic companies because neither of the individual components is patented in India today. However, Gilead has applied for patents related to TDF, which if granted will affect the production of not only TDF but also of this combination.

For further details on the patent status of TDF in India and Brazil, the voluntary licences agreements signed by Gilead and generic companies, and the Brazilian initiative for local production, please refer to the tenofovir drug profile.

### Paediatrics

TDF is approved for adolescents from 12 years old and 3TC is approved for use in children. Both medicines have the advantage of once-daily dosing.

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. Having safety and efficacy data in paediatric populations would enable children to stay longer on the same treatment regimen, and would facilitate harmonisation with adult regimens, as TDF-based first-line regimens are also the preferred option for adults.

However, no paediatric fixed-dose combination has been developed with TDF and 3TC.

There is an urgent need to have this combination developed for HIV and hepatitis B co-infected paediatric patients, for whom no treatment options currently exist.

The Paediatric Antiretroviral Working Group of WHO considers the development of a fixed-dose combination of TDF/3TC 75/75mg tablet and a scored 300/300mg tablet to be a high priority.<sup>22</sup>

# TENOFOVIR DISOPROXIL FUMARATE/ LAMIVUDINE/EFVIRENZ (TDF/3TC/EFV)

## GENERAL INFORMATION

- Therapeutic class: One NtRTI, one NRTI and one NNRTI in a triple fixed-dose combination.
- WHO guidelines: Indicated for first-line for adults and adolescents.<sup>6</sup>
- Originator company and product brand name: No originator product exists.
- First approval by U.S. Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Individual medicines included in 17th edition. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.<sup>24</sup>
- Patents: Most patents related to tenofovir (TDF), lamivudine (3TC) or to efavirenz (EFV) also affect this combination. In addition, other patents may have been applied for more specifically related to the use of these medicines in combination, or to this specific FDC.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

	Daily dose	Cipla	Matrix (CF)
Who can access this price?		See annex 2	
TDF/3TC/EFV 300/300/600mg tablet	1	195 (0.533)	<b>173 (0.475)</b>

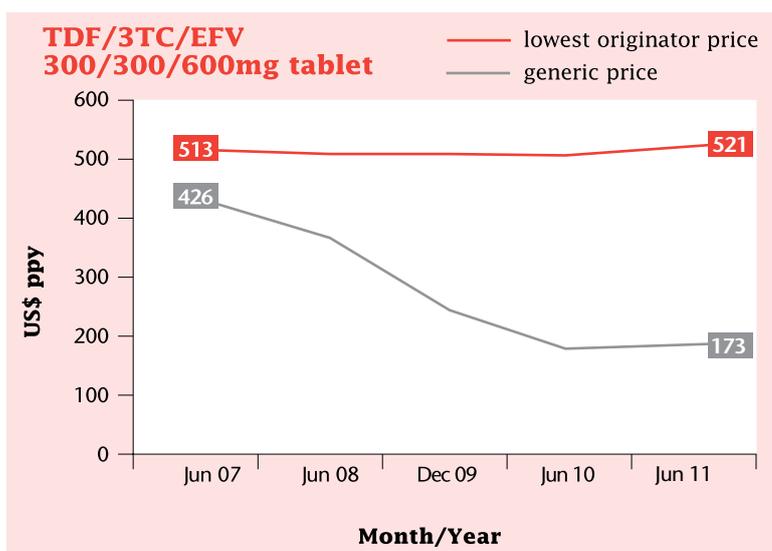
(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest quoted price for developing countries since 2007:

As of May 2011, one generic source of TDF/3TC/EFV 300/300/600mg tablet was quality-assured by US FDA or WHO prequalification. Its price is shown here.

As there is no originator fixed-dose combination or co-pack, the price shown for the originator product is the sum of the three individual originator products.

Since 2007, the sum of the originator prices has remained practically stable, while generic prices have dropped by 59%.



Continued overleaf ❖

## SPOTLIGHT ON ACCESS ISSUES

This is a one-pill-a-day fixed-dose combination, which makes it well-adapted to resource-poor settings, and likely to be widely used in developing countries as first-line regimen. It is also more affordable than TDF/FTC/EFV.

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine- (d4T) based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir- (TDF) based first-line regimens.

For many years, the regimen containing d4T played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and most importantly its low cost. d4T remains a widely used ARV in first-line regimens.

It is time for countries to invest in a more robust, TDF-containing first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which are both one pill, once a day or TDF/3TC + NVP (available in co-pack). While the price today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition and the economies of scale needed to further decrease prices.<sup>7</sup>

In addition, EFV is the preferred NNRTI for use in patients starting ART while on tuberculosis treatment.

### Patents

This combination is produced by Indian generic companies because none of the individual components is patented in India today. However, Gilead has applied for patents related to TDF, which if granted will affect the production of not only TDF but also of this combination.

For further details on the patent status of TDF in India and Brazil, the voluntary licences agreements signed by Gilead and generic companies, and the Brazilian initiative for local production, please refer to the tenofovir drug profile.

### Paediatrics

TDF is approved for adolescents from 12 years old, 3TC is approved for use in children, and EFV is approved for use in children above three years old. All three medicines have the advantage of once-daily dosing.

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. Having safety and efficacy data in paediatric populations would enable children to stay longer on the same treatment regimen, and would facilitate harmonisation with adult regimens, as TDF-based first-line regimens are also the preferred option for adults.

However, no paediatric fixed-dose combination has been developed with TDF, 3TC and EFV.

There is an urgent need to have this combination developed for HIV and hepatitis B co-infected paediatric patients, for whom no treatment options currently exist, as well as for HIV/TB co-infected young children who cannot be given NVP because of interactions between NVP and TB drugs.

As there is still no established dosing of EFV for children less than three years of age, there is an urgent need to establish the dosing of EFV for this age group for children with HIV/TB co-infection.

# TENOFOVIR DISOPROXIL FUMARATE/ LAMIVUDINE/NEVIRAPINE (TDF/3TC + NVP)

## GENERAL INFORMATION

- Therapeutic class: One NtRTI and one NRTI (in a double fixed-dose combination) + one NNRTI in a co-pack.
- WHO guidelines: Indicated for first-line for adults and adolescents.<sup>6</sup>
- Originator company and product brand name: No originator product exists.
- First approval by U.S. Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Individual medicines included in 17th edition. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.<sup>24</sup>
- Patents: Most patents related to tenofovir (TDF), lamivudine (3TC) or to nevirapine (NVP) also affect this combination.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one kit of three tablets. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

	Daily dose	Matrix
Who can access this price?		See annex 2
TDF/3TC + NVP 300/300 + 200mg (co-pack)	1 kit (3 tablets)	<b>134 (0.367)</b>

## SPOTLIGHT ON ACCESS ISSUES

This co-pack is likely to be widely used in developing countries as first-line regimen.

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine- (d4T) based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir- (TDF) based first-line regimens.

For many years, the regimen containing d4T played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and most importantly its low cost. d4T remains a widely used ARV in first-line regimens.

It is time for countries to invest in a more robust, TDF-containing first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which are both one pill, once a day or TDF/3TC + NVP (available in co-pack). While the price

today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition and the economies of scale needed to further decrease prices.<sup>7</sup>

However NVP interacts with one of the most commonly used TB drugs, rifampicin, requiring a switch to EFV during the course of TB treatment.

# ZIDOVUDINE/ LAMIVUDINE (AZT/3TC)

## GENERAL INFORMATION

- Therapeutic class: Two NRTI in a double fixed-dose combination.
- WHO guidelines: Indicated for first- and second-line for adults, adolescents and children.<sup>6,22</sup>
- Originator company and product brand name: GlaxoSmithKline (GSK), Combivir. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): September 1997.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Included in the 17th edition. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.<sup>24</sup>
- World sales of originator product: 2010: US\$ 588 million; 2009: \$649 million; 2008: \$713 million; 2007: \$888 million; 2006: \$1 billion; 2005: \$1.1 billion; 2004: \$1.1 billion.<sup>163, 25, 26, 27, 28, 29, 30</sup>
- Patents: Most patents related to zidovudine (AZT) or to lamivudine (3TC) also affect this combination. In addition, GSK applied for patents specifically related to the use of AZT and 3TC in combination,<sup>313</sup> and for the tablet formulation of the FDC,<sup>314</sup> which are due to expire in 2012 and 2017, respectively.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

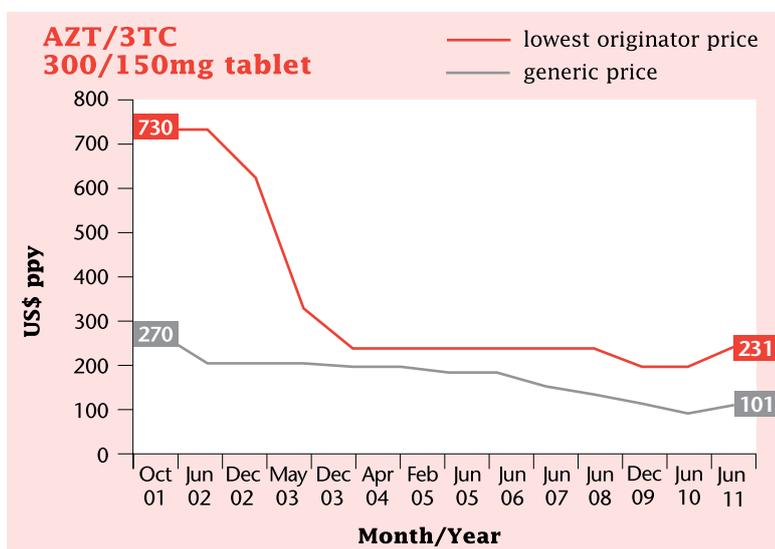
	Daily dose	ViiV	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Micro Labs (CF)	Ranbaxy (CF)	Strides	Varichem
Who can access this price?		See annex 2								
AZT/3TC 60/30mg tablet	4		<b>92 (0.063)</b>			<b>73 (0.050)</b>		88 (0.060)		
AZT/3TC 300/150mg tablet	2	<b>231 (0.316)</b>	<b>107 (0.147)</b>	<b>104 (0.142)</b>	<b>110 (0.150)</b>	<b>101 (0.138)</b>	<b>112 (0.154)</b>	<b>110 (0.150)</b>	<b>123 (0.169)</b>	<b>107 (0.147)</b>

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest price quoted for developing countries since 2001:

As of May 2011, 11 generic sources of AZT/3TC 300/150mg tablet were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

Since 2001, the originator price has decreased by 68%, while generic prices have dropped by 63%.



## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine- (d4T) based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir- (TDF) based first-line regimens.

For many years, the regimen containing d4T played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and most importantly its low cost. d4T remains a widely used ARV in first-line regimens.

AZT is also recommended for second-line treatment if tenofovir has been used in first-line. AZT should then be used as the NRTI backbone, in combination with either lamivudine (3TC) or emtricitabine (FTC), to which a boosted protease inhibitor (PI) should be added.

In 2011, ViiV clarified their pricing structure (see annex 2), confirming that their differential prices 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 those prices, and will have to negotiate prices on a case-by-case basis.

### Patents

This combination was produced by Indian generic companies because none of the individual components was patented in India. However, these generic versions came under threat when India began granting patents on pharmaceuticals in 2005, as GSK had applied for a patent on the combination.<sup>315,316</sup>

Civil society organisations in India opposed the patent application in March 2006,<sup>317</sup> which resulted in GSK communicating in August 2006 that patents specifically related to the fixed-dose combination were being withdrawn in all countries.<sup>318</sup>

Yet in some countries, generic versions of the FDC are not available because of GSK patent rights. In China, for example, GSK's exclusive rights on 3TC alone have led to the fact that only the originator product is available at \$1,839 per patient per year.

### Paediatrics

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends AZT/3TC as one of the possible combinations to be given with either an NNRTI or a PI in the first-line. The combination can also be part of second-line regimens, depending on what has been used as a first-line.<sup>22</sup>

AZT/3TC, when used with NVP, is part of one of the two most commonly used first-line regimens

for children today (the other being d4T/3TC/NVP). With both of these regimens, there is a need to start NVP at a lower dose for the first two weeks to minimise the side effects. Quality-assured double fixed-dose combinations are therefore of great value in allowing children to be safely and accurately dosed while starting treatment. In their absence, the alternative is to use two different syrups, which can be difficult to administer.

Because of the long-term risks of toxicity, particularly lipodystrophy in children treated with d4T-containing regimens, the use of AZT is preferred. Toxicity risks are also associated with AZT, with possible anaemia developing over the first few months of therapy, but the drug remains much better tolerated than d4T.<sup>22</sup> WHO guidelines recommend a preferential order of NRTIs to be used in first-line regimens, with AZT preferred over ABC, and ABC preferred over d4T.

As of May 2011, two paediatric AZT/3TC fixed-dose combination tablets were quality-assured by either US FDA or WHO prequalification.

# ZIDOVUDINE/LAMIVUDINE/ ABACAVIR (AZT/3TC/ABC)

## GENERAL INFORMATION

- Therapeutic class: Three NRTI in a triple fixed-dose combination.
- WHO guidelines: Indicated under specific conditions in adults, adolescents and children.<sup>6,22</sup>
- Originator company and product brand name: GlaxoSmithKline (GSK), Trizivir. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): November 2000.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Individual medicines included in 17th edition. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.<sup>24</sup>
- World sales of originator product: 2010: US\$ 233 million; 2009: \$307 million; 2008: \$350 million; 2007: \$455 million; 2006: \$529 million; 2005: \$598 million; 2004: \$635 million.<sup>163, 25, 26, 27, 28, 29, 30</sup>
- Patents: Most patents on zidovudine (AZT), lamivudine (3TC), AZT/3TC or abacavir (ABC) also affect this combination. In addition, GSK applied for patents more specifically related to the triple combination.<sup>308</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

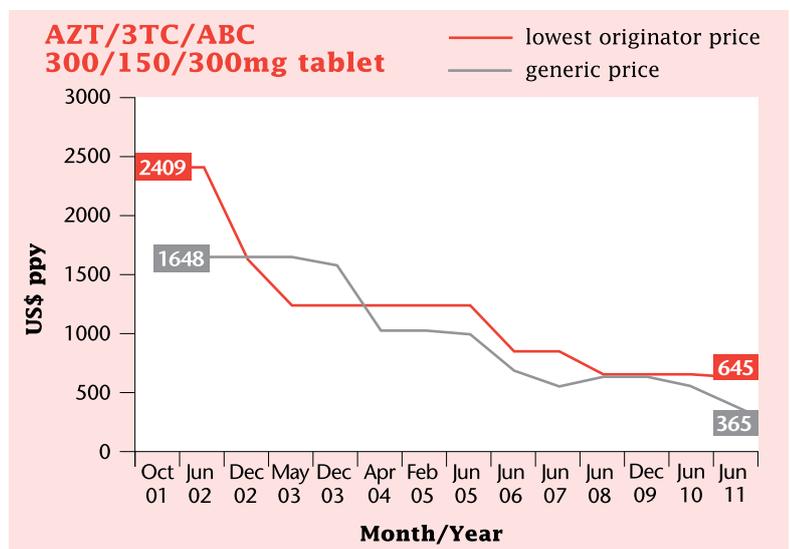
The price in brackets corresponds to the price of one tablet. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

	Daily dose	ViiV	Matrix	Ranbaxy
Who can access this price?		See annex 2		
AZT/3TC/ABC 60/30/60 mg tablet	4		<b>244</b> <b>(0.167)</b>	
AZT/3TC/ABC 300/150/300 mg tablet	2	<b>645</b> <b>(0.884)</b>	<b>365</b> <b>(0.500)</b>	<b>548</b> <b>(0.750)</b>

### Evolution of the lowest price quoted for developing countries since 2001:

As of May 2011, two generic source of AZT/3TC/ABC 300/150/300mg tablet were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

Since 2002, the originator price has decreased by 73%, while generic prices have dropped by 78%.



## SPOTLIGHT ON ACCESS ISSUES

This FDC is the only triple NRTI formulation available, and is no longer a preferred regimen in the developed world,<sup>320</sup> where its use is limited to individuals with contra-indication to NNRTI-based regimens or who are unable to tolerate them. This applies particularly to people co-infected with TB/HIV, pregnant women, patients with chronic viral hepatitis and those with HIV-2 infection.<sup>22</sup>

In 2011, ViiV clarified their pricing structure (see annex 2), confirming that their differential prices 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 those prices, and will have to negotiate prices on a case-by-case basis.

### Patents

GSK could not apply for basic patents related to ABC, AZT or 3TC in some developing countries such as India, which did not grant patents on pharmaceuticals at the time. This allowed Indian generic companies to develop generic versions of each medicine, and of the combination.

However, GSK widely applied for patents in other developing countries, where possible.

In India, GSK had applied for patents more specifically related to the fixed-dose combination. The company withdrew the patent application after a pre-grant opposition was filed by civil society in 2006.<sup>321</sup>

### Paediatrics

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends AZT/3TC/ABC as an option for TB/HIV co-infected patients.<sup>22</sup> This is crucial for a small cohort of patients below three years of age, for whom dosing studies for EFV do not exist.

A generic paediatric formulation of AZT/3TC/ABC has been developed and quality-assured by WHO prequalification. However, this product is not commercially available yet because of insufficient demand.



# ZIDOVUDINE/LAMIVUDINE/ NEVIRAPINE (AZT/3TC/NVP)

## GENERAL INFORMATION

- Therapeutic class: Two NRTI + one NNRTI in a triple fixed-dose combination.
- WHO guidelines: Indicated for first-line for adults, adolescents and children.<sup>6,22</sup>
- Originator company and product brand name: No originator product exists.
- First approval by U.S. Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Included in the 17th edition. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.<sup>24</sup>
- Patents: Most patents related to zidovudine (AZT), lamivudine (3TC), AZT/3TC or to nevirapine (NVP) also affect this combination.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

	Daily dose	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Ranbaxy (CF)	Strides
Who can access this price?		See annex 2					
AZT/3TC/NVP 60/30/50mg tablet	4				<b>101</b> <b>(0.069)</b>	183 (0.125)	
AZT/3TC/NVP 300/150/200mg tablet	2	<b>144</b> <b>(0.197)</b>	<b>137</b> <b>(0.188)</b>	<b>143</b> <b>(0.196)</b>	<b>134</b> <b>(0.183)</b>	<b>140</b> <b>(0.192)</b>	<b>141</b> <b>(0.193)</b>

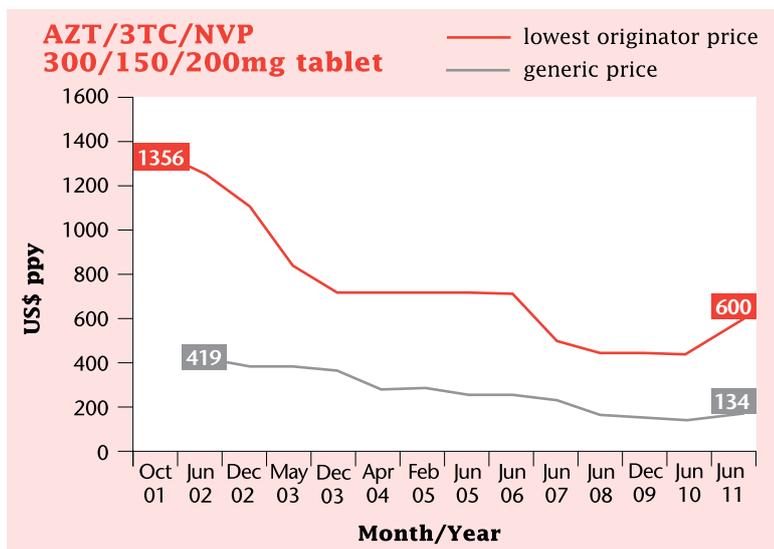
(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

### Evolution of the lowest price quoted for developing countries since 2001:

As of May 2011, six generic sources of AZT/3TC/NVP 300/150/200mg tablet were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

As there is no originator fixed-dose combination or co-pack, the price shown for the originator product is the sum of the three individual originator products.

Since 2002, the sum of the originator price has decreased by 56%, while generic prices have dropped by 68%.



## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine- (d4T) based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir- (TDF) based first-line regimens.

For many years, the regimen containing d4T has played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and most importantly its low cost. d4T remains a widely used ARV in first-line regimens.

### Patents

The Canadian generic company Apotex manufactures an AZT/3TC/NVP fixed-dose combination for export to developing countries under the 30 August 2003 World Trade Organization decision. The purpose of the August 30 Decision is to find an 'expeditious solution' to the problems of developing countries with no or insufficient manufacturing capacity and who therefore would rely on importing medicines produced in and exported from other countries, under compulsory licence.<sup>275</sup>

In early 2004, MSF made the original request for the development of this FDC to Apotex, as no generic versions of the FDC were available at the time.<sup>296</sup>

MSF, however, ultimately ended up procuring the FDC from manufacturers in India, which reached the market earlier because the Indian manufacturers were not hampered by the excessively bureaucratic procedural requirements of the new WTO rules on CL for export.

### Paediatrics

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends AZT/3TC as one of the possible combinations to be given with either an NNRTI or a PI in the first-line.<sup>22</sup>

Together with d4T/3TC/NVP, AZT/3TC/NVP is one of the two most commonly used first-line regimens for children today. With both of these regimens, there is a need to start NVP at a lower dose for the first two weeks to minimise the side effects, and therefore the AZT/3TC double fixed-dose combinations is of great value in allowing children to be safely and accurately dosed while starting treatment. In their absence, the alternative is to use two different syrups, which can be difficult to administer.

Because of the long-term risks of toxicity, particularly lipoatrophy in children treated with d4T-containing regimens, the use of AZT is preferred. Toxicity risks are also associated with AZT, with possible anaemia developing over the first few months of therapy, but the drug remains much better tolerated than d4T.<sup>22</sup> WHO guidelines recommend a preferential order of NRTIs to be used in first-line regimens, with AZT preferred over ABC, and ABC preferred over d4T.

HIV/TB co-infected young children cannot be given NVP because of interactions between NVP and TB drugs. As there is still no established dosing of EFV, the standard alternative to NVP, for children less than three years of age, there is an urgent need to establish the dosing of EFV for this age group.

As of May 2011, there was only one generic paediatric fixed-dose combination quality-assured by US FDA or WHO prequalification.

# ZIDOVUDINE/LAMIVUDINE + EFAVIRENZ (AZT/3TC + EFV)

## GENERAL INFORMATION

- Therapeutic class: Two NRTI (in a fixed-dose combination) + one NNRTI in a co-pack.
- WHO guidelines: Indicated for first-line for adults, adolescents and children.<sup>6,22</sup>
- Originator company and product brand name: No originator product exists.
- First approval by U.S. Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Individual medicines included in 17th edition. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.<sup>24</sup>
- Patents: Most patents related to zidovudine (AZT), lamivudine (3TC), AZT/3TC or to efavirenz (EFV) also affect this combination. In addition, Cipla applied for patents specifically related to the use of AZT, 3TC and EFV in combination.<sup>319</sup>

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one kit of three tablets. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

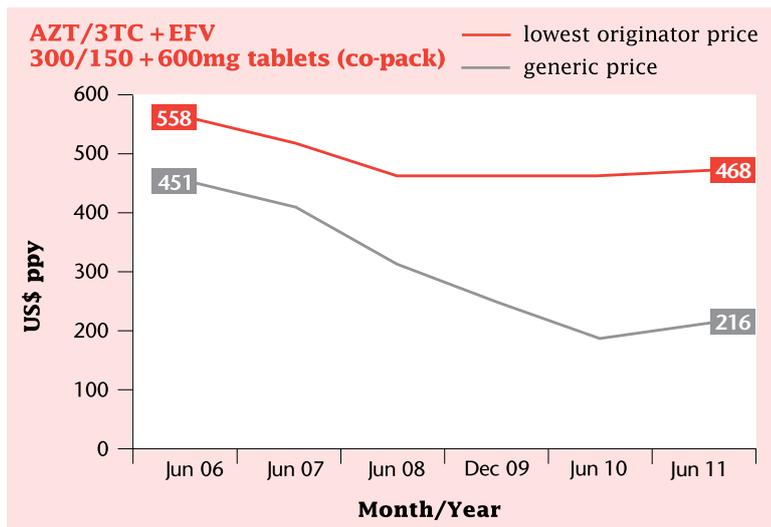
	Daily dose	Aurobindo	Ranbaxy	Strides
Who can access this price?		See annex 2		
AZT/3TC + EFV 300/150 + 600mg tablets (co-pack)	1 kit (3 tablets)	<b>216 (0.593)</b>	<b>292 (0.800)</b>	<b>225 (0.617)</b>

### Evolution of the lowest quoted price for developing countries since 2006:

As of May 2011, three generic sources of AZT/3TC + EFV 300/150 + 600mg tablets (co-pack) were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

As there is no originator co-pack, the price shown for the originator product is the sum of the two individual originator products.

Since 2006, the sum of the originator prices has decreased by 16%, while the generic prices have dropped by 52%.



## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine- (d4T) based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir- (TDF) based first-line regimens.

For many years, the regimen containing d4T played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and most importantly its low cost. d4T remains a widely used ARV in first-line regimens.

AZT is also recommended for second-line treatment if tenofovir has been used in first-line. AZT should then be used as the NRTI backbone, in combination with either lamivudine (3TC) or emtricitabine (FTC), to which a boosted protease inhibitor (PI) should be added.

In addition, efavirenz (EFV) is the preferred NNRTI for use in patients starting ART while on TB treatment.<sup>7</sup>

### Patents

Basic patents related to AZT, 3TC or EFV could not be obtained in some developing countries such as India, which did not grant product patents on pharmaceuticals at the time. This allowed Indian drug companies to manufacture generic versions of the medicines and to develop this product.

However, GlaxoSmithKline and Merck may hold patents in other developing countries, which could prevent the importation and use of this co-pack combination.

### Paediatrics

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends AZT/3TC as one of the possible combinations to be given with either an NNRTI or a PI in the first-line.<sup>22</sup>

Currently a co-pack of AZT/3TC + EFV for children does not exist.

Because of the long-term risks of toxicity, particularly lipoatrophy in children treated with d4T-containing regimens, the use of AZT is preferred. Toxicity risks are also associated with AZT, with possible anaemia developing over the first

few months of therapy, but the drug remains much better tolerated than d4T.<sup>22</sup> WHO guidelines recommend a preferential order of NRTIs to be used in first-line regimens, with AZT preferred over ABC, and ABC preferred over d4T.

As there is still no established dosing of EFV for children less than three years of age, there is an urgent need to establish the dosing of EFV for this age group for children with HIV/TB co-infection.

In the absence of such data, treatment options for children remain limited, particularly for HIV/TB co-infected young children who cannot be given NVP because of interactions between NVP and TB drugs.

## ANNEX 1: SUMMARY TABLE OF ALL PRICES

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one unit (tablet, capsule, etc.). Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

ARVs in alphabetical order	Daily dose	Originator company		Generic companies								
<b>Abacavir (ABC)</b>		ViiV		Aspen	Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides		
20mg/ml oral solution	10ml	<b>347</b> <b>(0.095/ml)</b>		153 (0.042/ml)	<b>212</b> <b>(0.058/ml)</b>	<b>139</b> <b>(0.038/ml)</b>						
60mg tablet	4				<b>146</b> <b>(0.100)</b>	<b>158</b> <b>(0.108)</b>		<b>134</b> <b>(0.092)</b>				
300mg tablet	2	<b>382</b> <b>(0.523)</b>			<b>195</b> <b>(0.267)</b>	<b>231</b> <b>(0.317)</b>	<b>231</b> <b>(0.317)</b>	<b>183</b> <b>(0.250)</b>	<b>261</b> <b>(0.358)</b>	<b>292</b> <b>(0.400)</b>		
<b>Atazanavir (ATV)*</b>		BMS		Emcure	Matrix							
		Category 1 countries	Category 2 countries									
100mg capsule	3			<b>(0.267)</b>								
150mg capsule	2	<b>412</b> <b>(0.565)</b>	<b>547</b> <b>(0.749)</b>	<b>268</b> <b>(0.367)</b>	<b>426</b> <b>(0.583)</b>							
200mg capsule	xx	(0.677)	(0.942)	<b>(0.483)</b>								
300mg capsule	1			<b>268</b> <b>(0.733)</b>	<b>250</b> <b>(0.686)</b>							
<b>Darunavir (DRV)*</b>		Tibotec										
300mg tablet	4	1095 (0.750)										
<b>Didanosine (ddl)</b>		BMS		Aurobindo	Cipla	Matrix	Ranbaxy					
		Category 1 countries	Category 2 countries									
2g powder for reconstitution (final concentration 10mg/ml)	12ml	<b>276</b> <b>(12.590/2g)</b>	<b>No discount</b>									
25mg tablet	6	<b>256</b> <b>(0.117)</b>	<b>No discount</b>		138 (0.063)		252 (0.115)					
50mg tablet	xx	<b>(0.159)</b>	<b>No discount</b>		(0.079)		(0.125)					
100mg tablet	xx	<b>(0.213)</b>	<b>No discount</b>	<b>(0.133)</b>	(0.129)		(0.166)					
125mg enteric-coated capsule	1			<b>110</b> <b>(0.300)</b>		<b>119</b> <b>(0.325)</b>						
150mg tablet	xx			<b>(0.225)</b>	(0.167)							
200mg tablet	xx			<b>(0.267)</b>	(0.257)							
200mg enteric-coated capsule	xx			<b>(0.383)</b>		<b>(0.489)</b>						
250mg enteric-coated capsule	1	<b>223</b> <b>(0.612)</b>	<b>316</b> <b>(0.866)</b>	<b>170</b> <b>(0.467)</b>	103 (0.283)	<b>172</b> <b>(0.467)</b>	134 (0.367)					
400mg enteric-coated capsule	1	<b>288</b> <b>(0.789)</b>	<b>408</b> <b>(1.118)</b>	<b>256</b> <b>(0.700)</b>	132 (0.363)	<b>268</b> <b>(0.733)</b>	183 (0.500)					
<b>Efavirenz (EFV)</b>		Merck		Aspen	Aurobindo	Cipla	Emcure	Hetero	Matrix	Micro Labs	Ranbaxy	Strides
		Category 1 countries	Category 2 countries									
30mg/ml suspension	xx	<b>(0.094/ml)</b>	<b>No discount</b>									
50mg capsule	xx				<b>(0.083)</b>					(0.047)		
50mg tablet	xx	<b>(0.120)</b>	<b>No discount</b>						<b>(0.050)</b>			
100mg capsule	xx									(0.042)		
100mg tablet	xx								<b>(0.117)</b>		(0.150)	
200mg capsule	3				<b>116</b> <b>(0.106)</b>	<b>134</b> <b>(0.122)</b>		152 (0.139)	80 (0.073)		<b>97</b> <b>(0.089)</b>	
200mg tablet	3	<b>394</b> <b>(0.360)</b>	<b>No discount</b>						<b>183</b> <b>(0.167)</b>			<b>113</b> <b>(0.103)</b>
600mg tablet	1	<b>237</b> <b>(0.650)</b>	<b>No discount</b>	62 (0.170)	<b>73</b> <b>(0.200)</b>	<b>79</b> <b>(0.217)</b>	<b>61</b> <b>(0.167)</b>	<b>67</b> <b>(0.183)</b>	<b>55</b> <b>(0.150)</b>	58 (0.158)	<b>72</b> <b>(0.197)</b>	<b>52</b> <b>(0.143)</b>

\*The required addition of RTV as a booster must also be considered in the final cost of this drug.

ARVs in alphabetical order	Daily dose	Originator company		Generic companies								
<b>Emtricitabine (FTC)</b>				Aurobindo	Cipla							
200mg capsule	1			<b>61</b> <b>(0.167)</b>	<b>97</b> <b>(0.267)</b>							
<b>Etravirine (ETV)</b>		Tibotec										
100mg tablet	4	913 (0.625)										
<b>Fosamprenavir (FPV)*</b>		ViiV										
50mg/ml suspension	12ml	837 (0.191/ml)										
700mg tablet	2	1131 (1.549)										
<b>Indinavir (IDV)*</b>		Merck										
		Category 1 countries	Category 2 countries	Aurobindo	Cipla	Hetero						
400mg capsule	4	<b>394</b> <b>(0.270)</b>	<b>No discount</b>	292 (0.200)	422 (0.289)	<b>406</b> <b>(0.278)</b>						
<b>Lamivudine (3TC)</b>		ViiV		Alkem	Aspen	Aurobindo	Cipla	Hetero	Matrix	Micro Labs	Ranbaxy	Strides
10mg/ml oral solution	10ml	<b>212</b> <b>(0.058/ml)</b>			33 (0.009/ml)	<b>29</b> <b>(0.008/ml)</b>	<b>55</b> <b>(0.015/ml)</b>	37 (0.010/ml)				
150mg tablet	2	<b>80</b> <b>(0.109)</b>		<b>42</b> <b>(0.058)</b>	<b>29</b> <b>(0.040)</b>	<b>34</b> <b>(0.047)</b>	<b>33</b> <b>(0.045)</b>	<b>33</b> <b>(0.045)</b>	<b>31</b> <b>(0.042)</b>	31 (0.042)	<b>34</b> <b>(0.047)</b>	<b>29</b> <b>(0.040)</b>
300mg tablet	1					<b>24</b> <b>(0.067)</b>	<b>41</b> <b>(0.113)</b>	<b>38</b> <b>(0.103)</b>		26 (0.071)		
<b>Lopinavir/ ritonavir (LPV/r)</b>		Abbott										
		Category 1 countries	Category 2 countries	Aurobindo	Cipla	Hetero	Matrix					
80/20mg/ml oral solution	4ml	<b>164</b> <b>(0.112/ml)</b>	<b>400</b> <b>(0.274/ml)</b>		256 (0.175/ml)							
100/25mg tablet (heat-stable)	3	<b>153</b> <b>(0.140)</b>	<b>376</b> <b>(0.343)</b>	<b>175</b> <b>(0.160)</b>				<b>164</b> <b>(0.150)</b>				
133/33mg soft-gel capsule (non heat-stable)	6	<b>500</b> <b>(0.228)</b>	<b>1000</b> <b>(0.457)</b>		633 (0.289)							
200/50mg tablet (heat-stable)	4	<b>410</b> <b>(0.281)</b>	<b>1000</b> <b>(0.457)</b>	<b>438</b> <b>(0.300)</b>	<b>499</b> <b>(0.342)</b>	493 (0.338)	<b>402</b> <b>(0.275)</b>					
<b>Maraviroc (MVC)</b>		ViiV										
150mg tablet	4	1584 (1.085)										
<b>Nelfinavir (NFV)</b>		Roche										
		Category 1 countries	Category 2 countries									
50mg/g oral powder	24g	<b>2742</b> <b>(0.313/g)</b>	<b>3171</b> <b>(0.362/g)</b>									
250mg tablet	10	<b>2018</b> <b>(0.553)</b>	<b>3132</b> <b>(0.858)</b>									
<b>Nevirapine (NVP)</b>		Boehringer Ingelheim										
		Category 1 countries	Category 2 countries	Aspen	Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides		
10mg/ml suspension	20ml	<b>380</b> <b>(0.052/ml)</b>	<b>533</b> <b>(0.073/ml)</b>		<b>58</b> <b>(0.008/ml)</b>	<b>110</b> <b>(0.015/ml)</b>						
200mg tablet	2	<b>219</b> <b>(0.300)</b>	<b>438</b> <b>(0.600)</b>	<b>37</b> <b>(0.051)</b>	<b>37</b> <b>(0.050)</b>	<b>39</b> <b>(0.054)</b>	<b>37</b> <b>(0.050)</b>	<b>31</b> <b>(0.043)</b>	<b>37</b> <b>(0.050)</b>	<b>32</b> <b>(0.044)</b>		
<b>Raltegravir (RAL)</b>		Merck										
		Category 1 countries	Category 2 countries									
400mg tablet	2	<b>675</b> <b>(0.925)</b>	<b>No discount</b>									

\*The required addition of RTV as a booster must also be considered in the final cost of this drug.

ARVs in alphabetical order	Daily dose	Originator company		Generic companies							
<b>Ritonavir (RTV)</b>		Abbott		Matrix							
		Category 1 countries	Category 2 countries								
80mg/ml oral solution	xx	<b>(0.093/ml)</b>	<b>No discount</b>								
100mg soft-gel capsule (non heat-stable)	2**	<b>83 (0.114)</b>	<b>No discount</b>								
100mg heat-stable tablet	2**	<b>83 (0.114)</b>	<b>No discount</b>	<b>183 (0.250)</b>							
<b>Saquinavir (SQV)*</b>		Roche									
		Category 1 countries	Category 2 countries								
200mg hard capsule	10	<b>1566 (0.429)</b>	<b>3132 (0.858)</b>								
500mg tablet	4	<b>1435 (0.983)</b>	<b>3130 (2.144)</b>								
<b>Stavudine (d4T)</b>		BMS		Aspen	Aurobindo	Cipla	Hetero	Ranbaxy	Strides		
		Category 1 countries	Category 2 countries								
1mg/ml powder for oral solution	20ml	<b>58 (0.008/ml)</b>	<b>No discount</b>		<b>58 (0.008/ml)</b>	<b>51 (0.007/ml)</b>					
15mg capsule	xx	<b>(0.083)</b>	<b>(0.118)</b>	(0.027)	<b>(0.024)</b>		<b>(0.025)</b>				
20mg capsule	xx	<b>(0.094)</b>	<b>(0.118)</b>	<b>(0.031)</b>	<b>(0.025)</b>		<b>(0.028)</b>				
30mg capsule	2	<b>48 (0.066)</b>	<b>86 (0.118)</b>		<b>20 (0.027)</b>		<b>21 (0.029)</b>	<b>24 (0.033)</b>	<b>22 (0.030)</b>		
<b>Tenofovir (TDF)</b>		Gilead		Aspen	Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides	
		Category 1 countries	Category 2 countries								
300mg tablet	1	<b>204 (0.559)</b>	<b>360 (0.986)</b>	87 (0.237)	<b>88 (0.242)</b>	<b>83 (0.227)</b>	<b>103 (0.283)</b>	<b>76 (0.208)</b>	<b>97 (0.267)</b>	79 (0.217)	
<b>Zidovudine (AZT)</b>		ViiV		Aspen	Aurobindo	Cipla	Hetero	Matrix	Micro Labs	Ranbaxy	
10mg/ml oral solution	20ml	<b>380 (0.052/ml)</b>		88 (0.012/ml)	<b>66 (0.009/ml)</b>	<b>110 (0.015/ml)</b>	73 (0.010/ml)				
60mg tablet	4				<b>115 (0.079/ml)</b>						
100mg capsule	xx	<b>(0.185)</b>			<b>(0.048)</b>	<b>(0.055)</b>					
250mg capsule	xx	<b>(0.301)</b>									
300mg tablet	2	<b>301 (0.412)</b>		<b>99 (0.136)</b>	<b>88 (0.121)</b>	<b>91 (0.125)</b>	<b>100 (0.137)</b>	<b>88 (0.121)</b>	<b>91 (0.125)</b>	<b>91 (0.125)</b>	
<b>ABC/3TC</b>		ViiV		Aurobindo	Matrix						
60/30mg tablet	4			<b>175 (0.120)</b>	<b>292 (0.200)</b>						
600/300mg tablet	1	388 (1.064)		<b>112 (0.308)</b>	<b>280 (0.767)</b>						
<b>3TC/d4T</b>				Cipla	Hetero	Matrix	Ranbaxy	Strides			
30/6mg dispersible tablet	4			<b>47 (0.032)</b>							
60/12mg dispersible tablet	2			<b>40 (0.055)</b>							
150/30mg tablet	2			<b>42 (0.058)</b>	<b>46 (0.063)</b>	<b>39 (0.054)</b>	<b>42 (0.058)</b>	<b>41 (0.056)</b>			
<b>3TC/d4T/NVP</b>				Cipla	Hetero	Ranbaxy	Strides	Varichem			
30/6/50mg dispersible tablet	4			<b>55 (0.038)</b>							
60/12/100mg dispersible tablet	2			<b>53 (0.072)</b>							
150/30/200mg tablet	2			<b>64 (0.088)</b>	<b>67 (0.092)</b>	<b>70 (0.096)</b>	<b>66 (0.090)</b>	<b>61 (0.083)</b>			

\*The required addition of RTV as a booster must also be considered in the final cost of this drug.

\*\*Dosing frequency depends on which drug RTV is used with as a booster.

ARVs in alphabetical order	Daily dose	Originator company		Generic companies								
<b>3TC/d4T + EFV (co-pack)</b>				Ranbaxy	Strides							
150/30 + 600mg tablets (co-pack)	1 kit (3 tablets)			<b>152 (0.417)</b>	106 (0.290)							
<b>TDF/FTC</b>		Gilead		Aurobindo	Cipla	Hetero	Matrix					
		Category 1 countries	Category 2 countries									
300/200mg tablet	1	<b>315 (0.863)</b>	<b>540 (1.479)</b>	<b>140 (0.383)</b>	134 (0.367)	164 (0.450)	<b>116 (0.317)</b>					
<b>TDF/FTC/EFV</b>		BMS/Gilead/Merck		Cipla	Hetero	Matrix						
		Category 1 countries	Category 2 countries									
300/200/600mg tablet	1	<b>613 (1.680)</b>	<b>1033 (2.830)</b>	231 (0.633)	243 (0.667)	<b>219 (0.600)</b>						
<b>TDF/3TC</b>				Aurobindo	Cipla	Hetero	Matrix					
300/300mg tablet	1			<b>116 (0.317)</b>	<b>103 (0.283)</b>	<b>116 (0.317)</b>	<b>91 (0.250)</b>					
<b>TDF/3TC/EFV</b>				Cipla	Matrix							
300/300/600mg tablet	1			195 (0.533)	<b>173 (0.475)</b>							
<b>TDF/3TC + NVP (co-pack)</b>				Matrix								
300/300 + 200mg tablets (co-pack)	1 kit (3 tablets)			<b>134 (0.367)</b>								
<b>AZT/3TC</b>		ViiV		Aurobindo	Cipla	Hetero	Matrix	Micro Labs	Ranbaxy	Strides	Varichem	
60/30mg tablet	4			<b>92 (0.063)</b>			<b>73 (0.050)</b>		88 (0.060)			
300/150mg tablet	2	<b>231 (0.316)</b>		<b>107 (0.147)</b>	<b>104 (0.142)</b>	<b>110 (0.150)</b>	<b>101 (0.138)</b>	<b>112 (0.154)</b>	<b>110 (0.150)</b>	<b>123 (0.169)</b>	<b>107 (0.147)</b>	
<b>AZT/3TC/ABC</b>		ViiV		Matrix	Ranbaxy							
60/30/60mg tablet	4			<b>244 (0.167)</b>								
300/150/300mg tablet	2	<b>645 (0.884)</b>		<b>365 (0.500)</b>	<b>548 (0.750)</b>							
<b>AZT/3TC/NVP</b>				Aurobindo	Cipla	Hetero	Matrix	Ranbaxy	Strides			
60/30/50mg dispersible tablet	4						<b>101 (0.069)</b>	183 (0.125)				
300/150/200mg tablet	2			<b>144 (0.197)</b>	<b>137 (0.188)</b>	<b>143 (0.196)</b>	<b>134 (0.183)</b>	<b>140 (0.192)</b>	<b>141 (0.193)</b>			
<b>AZT/3TC + EFV (co-pack)</b>				Aurobindo	Ranbaxy	Strides						
300/150 + 600mg tablets (co-pack)	1 kit (3 tablets)			<b>216 (0.593)</b>	<b>292 (0.800)</b>	<b>225 (0.617)</b>						

## ANNEX 2: CONDITIONS OF OFFER BY COMPANY

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Delivery of goods
<b>Abbott</b>	Category 1 countries: All African countries and all United Nations defined least-developed countries outside Africa.  Category 2 countries: See Annex 8 for more details.	Governments and programmes fully funded by governments, UN systems organisations, NGOs and other not-for-profit institutional providers in low and lower middle-income countries.		FOB.
<b>Alkem</b>	No restrictions.	No restrictions.		FCA Mumbai.
<b>Aspen</b>	South Africa public sector only.	South Africa public sector only.		Ex-works.
<b>Aurobindo</b>	No reported restrictions.	NGOs and governmental organisations.	Prices available for above 300,000 units for tablet packs and above 5,000 packs for oral solutions.  Delivery of goods 10-12 weeks from the date of confirmed orders.	Payment by letter of credit. FOB Hyderabad (India).
<b>Boehringer Ingelheim</b>	Category 1: All LDCs, all low-income countries and all of Africa.  Category 2: All middle-income countries not covered under category 1.	Governments, NGOs and other partners who can guarantee that the programme is run in a responsible manner.		CIF.
<b>Bristol-Myers Squibb</b>	Category 1 countries: Sub-Saharan African countries (except southern African countries) plus countries classified as low-income by the World Bank (except Korea, Kyrgyzstan, Moldova and Uzbekistan).  Category 2 countries: Southern African countries See annex 7 for more details.  For other developing countries, prices are negotiated on a case-by-case basis with BMS local representatives.	Both private and public sector organisations that are able to provide effective, sustainable and medically-sound care and treatment of HIV/AIDS.	Category 1 countries are invoiced in US\$.  Category 2 countries are invoiced in South African Rand.	CIP.
<b>Cipla</b>	No reported restrictions but higher prices have been negotiated separately for 10 Latin American countries.	No restrictions.	No quantity-related conditions. Prices for larger quantities are negotiable.	FOB Mumbai (India) or CIF. The actual freight is charged separately.

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Delivery of goods
<b>Emcure</b>	Only atazanavir is restricted to sales in India and sub-Saharan Africa. No restrictions for others.	No restrictions.		Ex-works.
<b>Gilead</b>	There are 130 eligible countries, including all African states and additional countries classified as low- or lower middle-income based on a country's economic status measure by gross national income (GNI) and HIV prevalence. See Annex 9 for more details. For other countries, prices are negotiated on a case-by-case basis.	Organisations that provide HIV treatment in 130 countries are covered by the Gilead Access Programme.	The programme is managed through Gilead's International Access Operations and Gilead's local distribution partners. Please note that local taxes, tariffs, and limited distributor mark-ups may be added to the ex-factory prices.	Shipping terms vary by local distributor.
<b>Hetero</b>	No reported restrictions.	Private sector, public sector and NGOs.	Prices may be negotiated on individual basis according to commercial terms.	FOB Mumbai (India).
<b>Matrix</b>	No reported restrictions except: Cuba, Iran, North Korea, Syria, Sudan, Belarus, Myanmar, Democratic Republic of Congo & Liberia for which prior approval from Mylan is required.	No restrictions.	Minimum order – One full shipper / carton packs.	Ex-works Nashik, India or as specified by customers.
<b>Merck</b>	All countries in sub-Saharan Africa and low- income countries based on World Bank country classification. Countries classified as lower-middle and upper-middle income by the World Bank will be eligible for prices that are discounted from the prices in the developed high income countries. These prices will vary based on country income, disease burden, and will be negotiated with each government. Please refer to Annex 10 for the individual drug country eligibility.	Governments and programmes fully funded by governments and /or by multi- and bi-lateral donors (i.e., Global Fund, PEPFAR, or UNITAID), UN System Organisations, NGOs and other non-commercial providers of HIV treatment.	Additional costs may include freight, insurance, customs handling, taxes and duties.	DDU, CIP or CPT airport of destination basis. (Incoterms, 2000).
<b>Micro Labs</b>	All countries except India.	All organisations / bodies except India.	Prices are subject to change due to fluctuation in active pharmaceutical ingredient price and exchange rate.	Ex-works.
<b>Ranbaxy</b>	No reported restrictions, but higher prices were negotiated separately for 10 Latin American countries.	NGOs and governments or programmes supported by them.	Confirmed letter of credit or advance payment preferred for new customers.	FCA Delhi (India).

Company	Eligibility (countries)	Eligibility (bodies)	Additional comments	Delivery of goods
<b>Roche</b>	<p>Category 1 countries: All countries in sub-Saharan Africa and all countries classified as least-developed countries by the United Nations.</p> <p>Category 2 countries: Low-income countries and lower middle-income countries, as classified by the World Bank.</p>	Governments, non-profit institutional providers of HIV care, NGOs.	CAD (Cash Against Documents) 30 days at sight. Minimum order and delivery amount per shipment is CHF 10,000.	FCA Basel airport (Switzerland) or CIP airport of destination. (Incoterms, 2000).
<b>Strides Arcolab</b>	No reported restrictions.	Governments, non-profit institutional providers of HIV treatment, NGOs.	Payment by signed letter of credit.	FOB Bangalore (India).
<b>Tibotec</b>	<p>Sub-Saharan Africa and least-developed countries (LDCs).</p> <p>For other low- and middle-income countries, public sector prices are negotiated on a case-by-case basis.</p>	No restrictions.	Questions regarding prices applied in the related countries need to be addressed to Aspen.	FOB.
<b>Varichem</b>	No restrictions.	No restrictions.	Prices are dependent on quantities being ordered.	FOB (Harare).
<b>ViiV</b>	<p>Least-developed countries, low-income countries and sub-Saharan Africa.</p> <p>All Country Coordination Mechanisms (CCM) projects in low-income countries, least-developed countries and countries in sub-Saharan Africa fully financed by the Global Fund to Fight AIDS, TB and Malaria, as well as projects funded by PEPFAR.</p> <p>For middle-income countries, public sector prices are negotiated on a case-by-case basis, either bilaterally or through the Accelerating Access Initiative.</p>	<p>Governments, aid organisations, charities, UN agencies, other not-for-profit organisations and international procurement agencies.</p> <p>In sub-Saharan Africa, employers offering HIV/AIDS care and treatment directly to their uninsured staff through workplace clinics or similar arrangements.</p>	<p>Supply Agreement required (for NGOs requiring fewer than ten patient packs per month, this requirement may be waived).</p> <p>All organisations must supply the preferentially priced products on a not-for-profit basis.</p>	All NFP prices are quoted ex-factory. Cost of delivery will be added to the ex-factory price.

**NOTES:**

The conditions detailed in the table above were those quoted directly by the companies. Definitions of eligibility vary from company to company. Each originator company establishes different restrictions to their offer of reduced prices, and classifies countries according to different categories. Some companies resort to least-developed country (LDC) criteria developed by the United Nations, others to the UN Development Programme's Human Development Index (UNDP HDI), and others still to World Bank classifications concerning country income.

For complete details please refer to annexes 3-10.

### ANNEX 3: LEAST-DEVELOPED COUNTRIES (LDCS)

Source: United Nations

<http://www.un.org/special-rep/ohrls/ldc/list.htm>

48 countries are currently designated by the United Nations as least-developed countries (LDCs).

Afghanistan; Angola; Bangladesh; Benin; Bhutan; Burkina Faso; Burundi; Cambodia; Central African Republic; Chad; Comoros; Congo (Democratic Republic); Djibouti; Equatorial Guinea; Eritrea; Ethiopia; Gambia; Guinea; Guinea-Bissau; Haiti; Kiribati; Laos; Lesotho; Liberia; Madagascar; Malawi; Mali; Mauritania; Mozambique; Myanmar; Nepal; Niger; Rwanda; Samoa; São Tomé and Príncipe; Senegal; Sierra Leone; Solomon Islands; Somalia; Sudan; Tanzania; Timor-Leste; Togo; Tuvalu; Uganda; Vanuatu; Yemen; Zambia.

### ANNEX 4: HUMAN DEVELOPMENT INDEX (HDI)

Source: United Nations Development Programme (UNDP) 2010 rankings

<http://hdr.undp.org/en/statistics/>

The Human Development Index is published annually as a part of UNDP's annual Human Development Report.

#### Low human development:

Afghanistan; Angola; Bangladesh; Benin; Burkina Faso; Burundi; Cameroon; Central African Republic; Chad; Comoros; Congo (Democratic Republic); Côte d'Ivoire; Djibouti; Ethiopia; Gambia; Ghana; Guinea; Guinea-Bissau; Haiti; Kenya; Lesotho; Liberia; Madagascar; Malawi; Mali; Mauritania; Mozambique; Myanmar; Nepal; Niger; Nigeria; Papua New Guinea; Rwanda; Senegal; Sierra Leone; Sudan; Tanzania; Togo; Uganda; Yemen; Zambia; Zimbabwe.

#### Medium human development:

Bolivia; Botswana; Cambodia; Cape Verde; China; Congo; Dominican Republic; Egypt; El Salvador; Equatorial Guinea; Fiji; Gabon; Guatemala; Guyana; Honduras; India; Indonesia; Kyrgyzstan; Laos; Maldives; Micronesia; Moldova;

Mongolia; Morocco; Namibia; Nicaragua; Pakistan; Paraguay; Philippines; Solomon Islands; South Africa; Sri Lanka; Suriname; Swaziland; Syria; São Tomé and Príncipe; Tajikistan; Thailand; Timor-Leste; Turkmenistan; Uzbekistan; Vietnam.

### ANNEX 5: SUB-SAHARAN COUNTRIES

Source: World Bank country classification

[http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS/0,,contentMDK:20421402~pagePK:64133150~piPK:64133175~theSitePK:239419,00.html#Sub\\_Saharan\\_Africa](http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS/0,,contentMDK:20421402~pagePK:64133150~piPK:64133175~theSitePK:239419,00.html#Sub_Saharan_Africa)

Angola; Benin; Botswana; Burkina Faso; Burundi; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo; Congo (Democratic Republic); Côte d'Ivoire; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Kenya; Lesotho; Liberia; Madagascar; Malawi; Mali; Mauritania; Mauritius; Mozambique; Namibia; Niger; Nigeria; Rwanda; São Tomé and Príncipe; Senegal; Seychelles; Sierra Leone; Somalia; South Africa; Sudan; Swaziland; Tanzania; Togo; Uganda; Zambia; Zimbabwe.

### ANNEX 6: WORLD BANK CLASSIFICATION OF ECONOMIES

Source: World Bank

<http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS/0,,contentMDK:20421402~pagePK:64133150~piPK:64133175~theSitePK:239419,00.html>

The list is updated every year on 1 July. This version is effective from 1 July 2010.

#### Low-income economies:

Afghanistan; Bangladesh; Benin; Burkina Faso; Burundi; Cambodia; Central African Republic; Chad; Comoros; Congo (Democratic Republic); Eritrea; Ethiopia; Gambia; Ghana; Guinea; Guinea-Bissau; Haiti; Kenya; Korea (Democratic Republic); Kyrgyzstan; Laos; Liberia; Madagascar; Malawi; Mali; Mauritania; Mozambique; Myanmar; Nepal; Niger; Rwanda; Sierra Leone; Solomon Islands; Somalia; Tajikistan; Tanzania; Togo; Uganda; Zambia; Zimbabwe.

#### Lower middle-income economies:

Angola; Armenia; Belize; Bhutan; Bolivia; Cameroon; Cape Verde; China; Congo (Rep); Côte d'Ivoire; Djibouti; Ecuador; Egypt; El Salvador; Georgia; Guatemala; Guyana; Honduras; India; Indonesia; Iraq; Jordan; Kiribati; Kosovo; Lesotho; Maldives; Marshall Islands; Micronesia; Moldova; Mongolia; Morocco; Nicaragua; Nigeria; Pakistan; Papua New Guinea; Paraguay; Philippines; Samoa; São Tomé and Príncipe; Senegal; Sri Lanka; Sudan; Swaziland; Syria; Thailand; Timor-Leste; Tonga; Tunisia; Turkmenistan; Tuvalu; Ukraine; Uzbekistan; Vanuatu; Vietnam; West Bank and Gaza; Yemen.

#### Upper middle-income economies:

Albania; Algeria; American Samoa; Antigua and Barbuda; Argentina; Azerbaijan; Belarus; Bosnia and Herzegovina; Botswana; Brazil; Bulgaria; Chile; Colombia; Costa Rica; Cuba; Dominica; Dominican Republic; Fiji; Gabon; Grenada; Iran; Jamaica; Kazakhstan; Lebanon; Libya; Lithuania; Macedonia; Malaysia; Mauritius; Mexico; Montenegro; Namibia; Palau; Panama; Peru; Romania; Russia; Serbia; Seychelles; South Africa; St. Kitts and Nevis; St. Lucia; St. Vincent and the Grenadines; Suriname; Turkey; Uruguay; Venezuela.

### ANNEX 7: BRISTOL- MYERS SQUIBB ELIGIBLE COUNTRIES

#### Category 1 Countries:

Afghanistan; Angola; Bangladesh; Benin; Bhutan; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo; Congo (Democratic Republic); Côte d'Ivoire; Djibouti; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Haiti; Kenya; Laos; Liberia; Madagascar; Mali; Mauritania; Mauritius; Mongolia; Myanmar; Nepal; Nicaragua; Niger; Nigeria; Pakistan; Papua New Guinea; Rwanda; São Tomé and Príncipe; Senegal; Seychelles; Sierra Leone; Solomon Islands; Somalia; South Sudan; Tanzania; Timor-Leste; Togo; Tuvalu; Uganda; Vietnam; Yemen.

#### Category 2 Countries:

##### Southern African countries:

Botswana; Lesotho; Malawi; Mozambique; Namibia; South Africa; Swaziland; Zambia; Zimbabwe.

## ANNEX 8: ABBOTT ELIGIBLE COUNTRIES

Source: Abbott's Access to HIV Care Program

### Category 1 countries:

#### Africa and Least-developed countries:

Afghanistan; Algeria; Angola; Bangladesh; Benin; Bhutan; Botswana; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo-Brazzaville; Côte d'Ivoire; Congo (Democratic Republic); Djibouti; East Timor; Egypt; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Haiti; Kiribati; Kenya; Laos; Lesotho; Liberia; Libya; Madagascar; Malawi; Maldives; Mali; Mauritania; Mauritius; Morocco; Mozambique; Myanmar; Namibia; Nepal; Niger; Nigeria; Rwanda; Samoa; São Tomé and Príncipe; Senegal; Seychelles; Sierra Leone; Solomon Islands; Somalia; South Africa; Sudan; Swaziland; Tanzania; Togo; Tunisia; Tuvalu; Uganda; Vanuatu; Yemen; Zambia; Zimbabwe.

### Category 2 countries:

#### Low-income economies (excluding Africa and the LDCs as defined by the UN)

India; Kyrgyzstan; Mongolia; Pakistan; Papua New Guinea; Tajikistan; Uzbekistan; Vietnam.

#### Lower middle-income economies (excluding Africa and the LDCs as defined by the UN)

Albania; Armenia; Azerbaijan; Belarus; Bolivia; Bosnia and Herzegovina; Brazil; China; Colombia, Dominican Republic; Ecuador; El Salvador; Fiji; Georgia; Guatemala; Guyana; Honduras; Indonesia; Jamaica; Jordan; Kazakhstan; FYR-Macedonia; Marshall Islands; Micronesia; Moldova; Montenegro; Nicaragua; Paraguay; Peru; Philippines; Serbia; Sri Lanka; Suriname; Syria; Thailand; Tonga; Turkmenistan; Ukraine.

## ANNEX 9: GILEAD ELIGIBLE COUNTRIES

Source: Gilead Access Program

[http://www.gilead.com/enabling\\_access](http://www.gilead.com/enabling_access)

### Category 1 countries:

#### Low-income pricing tier

Afghanistan; Algeria; Angola; Anguilla; Antigua and Barbuda; Bahamas; Bangladesh; Barbados; Belize; Benin; Bhutan; Bolivia; Botswana; British Virgin Islands; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo; Congo (Democratic Republic); Côte d'Ivoire; Cuba; Djibouti; Dominica; Dominican Republic; Egypt; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Grenada; Guatemala; Guinea; Guinea-Bissau; Guyana; Haiti; Honduras; India; Indonesia; Jamaica; Kenya; Kiribati; Kyrgyzstan; Laos; Lesotho; Liberia; Libya; Madagascar; Malawi; Maldives; Mali; Mauritania; Mauritius; Moldova; Mongolia; Montserrat; Morocco; Mozambique; Myanmar; Namibia; Nauru; Nepal; Nicaragua; Niger; Nigeria; Pakistan; Palau; Papua New Guinea; Rwanda; St. Kitts and Nevis; St. Lucia; St. Vincent and the Grenadines; Samoa; São Tomé and Príncipe; Senegal; Seychelles; Sierra Leone; Solomon Islands; Somalia; South Africa; Sudan; Suriname; Swaziland; Syria; Tajikistan; Tanzania; Timor-Leste; Togo; Trinidad and Tobago; Tunisia; Turks and Caicos; Tuvalu; Uganda; Ukraine; Uzbekistan; Vanuatu; Vietnam; Yemen; Zambia; Zimbabwe.

### Category 2 countries:

#### Lower middle-income pricing tier

Albania; Armenia; Azerbaijan; Belarus; Bosnia and Herzegovina; China; Ecuador; El Salvador; Fiji; Georgia; Iran; Iraq; Jordan; Kazakhstan; Kosovo; Montenegro; Panama; Paraguay; Peru; Philippines; Sri Lanka; Thailand; Tonga; Turkmenistan.

## ANNEX 10: MERCK ELIGIBLE COUNTRIES

Source: The following lists and notes are from correspondence with Merck.

### Merck's pricing policy efavirenz, indinavir and raltegravir

All countries in sub-Saharan Africa and Low-Income Countries based on World Bank country classification.

Afghanistan; Angola; Bangladesh; Benin; Botswana; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo; Congo (Democratic Republic); Cote d'Ivoire; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia, The; Ghana; Guinea; Guinea-Bissau; Haiti; Kenya; Korea Democratic Republic; Kyrgyzstan; Laos; Lesotho; Liberia; Madagascar; Malawi; Mali; Mauritania; Mauritius; Mozambique; Myanmar; Namibia; Nepal; Niger; Nigeria; Rwanda; São Tomé and Príncipe; Senegal; Seychelles; Sierra Leone; Solomon Islands; Somalia; South Africa; Sudan; Swaziland; Tajikistan; Tanzania; Togo; Uganda; Zambia; Zimbabwe.

### Merck's pricing policy for TDF/FTC/EFV

#### Category 1 countries:

Afghanistan; Angola; Antigua and Barbuda; Bangladesh; Belize; Benin; Bhutan; Botswana; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo; Congo (Democratic Republic); Côte d'Ivoire; Djibouti; Dominica; Dominican Republic; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Grenada; Guatemala; Guinea-Bissau; Guinea; Guyana; Haiti; Honduras; Jamaica; Kenya; Kiribati; Laos; Lesotho; Liberia; Madagascar; Malawi; Maldives; Mali; Mauritania; Moldova; Mozambique; Myanmar; Namibia; Nepal; Niger; Nigeria; Pakistan; Panama; Papua New Guinea; Rwanda; São Tomé and Príncipe; Senegal; Sierra Leone; Solomon Islands; Somalia; South Africa; St. Kitts and Nevis; St. Lucia; St. Vincent and the Grenadines; Sudan; Suriname; Swaziland; Tanzania; Timor-Leste; Togo; Trinidad and Tobago; Tuvalu; Uganda; Ukraine; Vanuatu; Western Samoa; Yemen; Zambia; Zimbabwe.

#### Category 2 countries:

Bolivia; Indonesia; Kyrgyzstan; Mauritius; Mongolia; Nicaragua; Seychelles; Syria; Tajikistan; Uzbekistan; Vietnam.

## ANNEX 11: SUGGESTED RESOURCES FOR FURTHER INFORMATION:

### For documentation on prices quoted by companies:

Untangling the Web can also be found online at [utw.msfacecess.org](http://utw.msfacecess.org)

Back issues of Untangling the Web of Price Reductions: A pricing guide for the purchase of ARVs for developing countries, can be found at: <http://utw.msfacecess.org/downloads>

Sources and Prices of Selected Medicines and Diagnostics for People Living with HIV/AIDS (June 2005) [http://www.who.int/medicines/areas/access/med\\_prices\\_hiv\\_aids/en/index.html](http://www.who.int/medicines/areas/access/med_prices_hiv_aids/en/index.html)

Global HIV/Aids Epidemic Selection of Antiretroviral Medications Provided under U.S. Emergency Plan Is Limited, January 2005: [http://pdf.dec.org/pdf\\_docs/Pcaab266.pdf](http://pdf.dec.org/pdf_docs/Pcaab266.pdf)

### For documentation on prices reported by countries:

WHO Global Price Reporting Mechanism <http://www.who.int/3by5/amds/price/hdd/>

The Global Fund Price Reporting Mechanism [http://www.theglobalfund.org/en/funds\\_raised/price\\_reporting/default.asp](http://www.theglobalfund.org/en/funds_raised/price_reporting/default.asp)

Management Sciences for Health (MSH) International Drug Price Indicator Guide <http://erc.msh.org/mainpage.cfm?file=1.0.htm&id=1&template=Introduction&module=DMP&language=English#top>

WHO AFRO Region Essential Medicines Price Indicator [http://www.who.int/medicines/publications/afro-essential\\_med\\_price\\_indicator\\_nocover.pdf](http://www.who.int/medicines/publications/afro-essential_med_price_indicator_nocover.pdf)

### For documentation on patents:

“Determining the patent status of essential medicines in developing countries”, Health Economics and Drugs, EDM Series No. 17, UNAIDS/WHO/MSF, 2004. [http://mednet2.who.int/sourcesprices/DeterminingEssMedPatentStatusW\\_Depliant.pdf](http://mednet2.who.int/sourcesprices/DeterminingEssMedPatentStatusW_Depliant.pdf)

HIV/AIDS medicines and related supplies: Contemporary context and procurement. Technical guide.

Chapter 2 and Annex B. World Bank, Washington, DC, 2004 <http://siteresources.worldbank.org/INTPROCUREMENT/Resources/Technical-Guide-HIV-AIDS.pdf>

“Drug patents under the spotlight. Sharing practical knowledge about pharmaceutical patents” MSF, June 2004. [http://www.who.int/3by5/en/patents\\_2003.pdf](http://www.who.int/3by5/en/patents_2003.pdf)

Knowledge Ecology International <http://www.keionline.org>, or <http://www.cptech.org/ip/health/>

The Patent Status Database for Selective HIV Medicines. Medicines Patent Pool [Online]. 2011. Available from: <http://www.medicinespatentpool.org/LICENSING/Patent-Status-of-ARVs>

### For documentation on quality:

Prequalification Programme managed by the World Health Organization (WHO) <http://mednet3.who.int/prequal/>

US Food and Drug Administration (FDA) Tentative Approvals <http://www.fda.gov/cder/ogd/approvals/>

### Other useful websites referenced in this document:

International Dispensary Association (IDA) Price Indicator [http://www.idafoundation.org/documents/ida\\_hiv\\_aids\\_aug\\_07\\_zondersnijlijnen.pdf](http://www.idafoundation.org/documents/ida_hiv_aids_aug_07_zondersnijlijnen.pdf)

US Food and Drug Administration Orange Book <http://www.fda.gov/cder/ob/>

Catalogue of US Food and Drug Administration Approved Drug Products <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>

WHO Registration <http://ftp.who.int/htm/AMDS/drugsdatabase.pdf>

WHO Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a public <http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf>

Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access: Recommendations for a public health approach 2007. <http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf>

UNICEF Procurement of HIV/AIDS Related Supplies. September 2007 [http://www.unicef.org/supply/files/Procurement\\_of\\_HA\\_supplies\(1\).pdf](http://www.unicef.org/supply/files/Procurement_of_HA_supplies(1).pdf)

Biotechnology/Pharmaceuticals HIV/AIDS Industry Report – April 2005 <http://www.aethlonmedical.com/pdfs/IndustryReport.pdf>

Clinton Health Access Initiative Antiretroviral Ceiling Price List [http://www.clintonfoundation.org/files/chai\\_arv\\_ceilingPriceList\\_201105\\_english.pdf](http://www.clintonfoundation.org/files/chai_arv_ceilingPriceList_201105_english.pdf)

MSF Campaign for Access to Essential Medicines website <http://www.msfacecess.org>

## ANNEX 12: COMPANY CONTACTS

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**E-mail:** access@gilead.com  
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access\\_developing\\_world](http://www.gilead.com/access_developing_world)

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## ANNEX 13: THE CLINTON HEALTH ACCESS INITIATIVE ANTIRETROVIRAL (ARV) PRICE LIST (AS OF MAY 2011)



**The Clinton Health Access Initiative (CHAI) supports national governments to expand high-quality care and treatment to people living with HIV/AIDS. CHAI offers reduced prices for antiretrovirals (ARVs) to members of its Procurement Consortium.**

### SUPPLIERS & PRODUCTS

CHAI has agreements with eight manufacturers of ARV formulations, active pharmaceutical ingredients and/or pharmaceutical intermediates: Aurobindo Pharma, Cipla Ltd., Emcure Pharmaceuticals, Hetero Drugs, Matrix Laboratories, Micro Labs Ltd., Ranbaxy Laboratories and Strides Arcolabs. The ARVs included in CHAI's pricing agreements are: abacavir (ABC), atazanavir (ATV), efavirenz (EFV), emtricitabine (FTC), lamivudine (3TC), lopinavir/ritonavir (LPV/r), nevirapine (NVP), ritonavir (RTV), stavudine (d4T), tenofovir (TDF) and zidovudine (AZT).

### TERMS & CONDITIONS

Prices listed below are available to countries participating in the CHAI Procurement Consortium, which currently includes over 70 nations. These prices apply to procurements by national governments that are members of the CHAI Procurement Consortium, or organizations procuring on behalf of member governments, to support public care and treatment programs. Products should be purchased directly from partner suppliers or through procurement agents representing the aforementioned programs. For TDF products offered by suppliers under a voluntary licence from Gilead, indicated pricing is available only to countries covered under the voluntary licence. Please contact Neeraj Mohan at [mneeraj@clintonhealthaccess.org](mailto:mneeraj@clintonhealthaccess.org) with any questions related to this issue.

Access to CHAI prices assumes prompt payment following the shipment of orders. Purchasers issuing requests for price quotes and/or tenders to which CHAI partner suppliers are invited to respond should reference membership in the CHAI Procurement Consortium, but requests and tenders need not be restricted to CHAI partner suppliers.

### PRICES

CHAI ceiling prices represent the maximum levels at which indicated suppliers may price their products when selling or communicating price quotes to members of the CHAI Procurement Consortium. CHAI notes that there may be, in several cases, opportunities to obtain lower prices as a result of higher volumes, greater competition, and other market factors. We encourage Consortium members to seek and take advantage of such opportunities and to base treatment decisions on observed market prices, with ceiling prices indicating the upper bounds of treatment costs. Prices listed below are FCA Airport from the point of export. Annual treatment costs for pediatric formulations are determined based on the recommended daily dosing for a 10 kg child (unless a formulation is not recommended for a 10kg child, in which case the annual price is calculated based on dosing for an applicable weight band).

### QUALITY

CHAI is committed to the sustainable supply of high-quality ARVs, consistent with the specifications of dossiers approved by the World Health Organization (WHO), U.S. Food and Drug Administration (U.S. FDA), or a stringent regulatory authority (SRA) as defined by the International Conference on Harmonization (ICH). In the list below, footnotes specify the applicable quality assurance status for each formulation: (1) Approved by the WHO Prequalification Programme; (2) Approved by the U.S. FDA or other SRA; (3) Submitted to the WHO, U.S. FDA or other SRA for review and recommended for procurement by Expert Review Panel (ERP) of The Global Fund; (4) Submitted to the WHO, U.S. FDA or other SRA for review but not yet recommended by ERP.

## THE CLINTON HEALTH ACCESS INITIATIVE — ANTIRETROVIRAL (ARV) PRICE LIST

ADULT PRODUCTS		CEILING PRICE (USD)			SUPPLIER						
Name and strength	Packaging	Per Year	Per Pack	Per Unit	Aurobindo	Cipla	Emcure	Hetero	Matrix	Ranbaxy	Micro
3TC (150mg)	HDPE bottle 60 tablets	\$32	\$2.6	\$0.044	✓ <sup>2</sup>	✓ <sup>1</sup>		✓ <sup>1,2</sup>	✓ <sup>1,2</sup>		✓ <sup>4</sup>
ABC (300mg)	HDPE bottle 60 tablets	\$210	\$17.5	\$0.292	✓ <sup>2</sup>	✓ <sup>1,2</sup>			✓ <sup>1,2</sup>		
AZT (300mg)	HDPE bottle 60 tablets	\$89	\$7.4	\$0.123	✓ <sup>2</sup>	✓ <sup>1,2</sup>		✓ <sup>1,2</sup>	✓ <sup>1,2</sup>		✓ <sup>1</sup>
AZT (300mg) + 3TC (150mg)	HDPE bottle 60 tablets	\$105	\$8.8	\$0.146	✓ <sup>2</sup>	✓ <sup>1,2</sup>		✓ <sup>1,2</sup>	✓ <sup>1,2</sup>	✓ <sup>1</sup>	✓ <sup>1</sup>
AZT (300mg) + 3TC (150mg) + NVP (200mg)	HDPE bottle 60 tablets	\$134	\$11.2	\$0.186	✓ <sup>2</sup>	✓ <sup>1,2</sup>		✓ <sup>1,2</sup>	✓ <sup>1,2</sup>	✓ <sup>1</sup>	
ATV (300mg)*	HDPE bottle 30 capsules	\$265	\$22.1	\$0.736			✓ <sup>2</sup>		✓ <sup>1,2</sup>		
d4T (30mg)	HDPE bottle 60 capsules	\$24	\$2.0	\$0.033	✓ <sup>2</sup>						
d4T (30mg) + 3TC (150mg)	HDPE bottle 60 tablets	\$45	\$3.8	\$0.063		✓ <sup>1,2</sup>		✓ <sup>2</sup>		✓ <sup>1</sup>	
d4T (30mg) + 3TC (150mg) + NVP (200mg)	HDPE bottle 60 tablets	\$79	\$6.6	\$0.110		✓ <sup>1,2</sup>		✓ <sup>1,2</sup>		✓ <sup>1</sup>	
EFV (600mg)	HDPE bottle 30 tablets	\$60	\$5.0	\$0.167	✓ <sup>2</sup>				✓ <sup>1,2</sup>		
LPV/r (200/50mg)	HDPE bottle 120 tablets	\$399	\$33.3	\$0.277	✓ <sup>2</sup>	✓ <sup>2</sup>			✓ <sup>1,2</sup>		
NVP (200mg)	HDPE bottle 60 tablets	\$36	\$3.0	\$0.050	✓ <sup>2</sup>	✓ <sup>1,2</sup>		✓ <sup>1,2</sup>	✓ <sup>1,2</sup>		
RTV (100mg) heat stable*	HDPE bottle 30 tablets	\$90	\$7.5	\$0.250					✓ <sup>1</sup>		
TDF (300mg)	HDPE bottle 30 tablets	\$78	\$6.5	\$0.217	✓ <sup>2</sup>	✓ <sup>1,2</sup>		✓ <sup>2</sup>	✓ <sup>1,2</sup>	✓ <sup>1</sup>	
TDF + 3TC (300/300mg)*	HDPE bottle 30 tablets	\$99	\$8.3	\$0.275	✓ <sup>2</sup>	✓ <sup>2</sup>		✓ <sup>2</sup>	✓ <sup>1,2</sup>		
TDF + FTC (300/200mg)	HDPE bottle 30 tablets	\$126	\$10.5	\$0.350	✓ <sup>2</sup>	✓ <sup>3</sup>			✓ <sup>1,2</sup>		
TDF + 3TC + EFV (300/300/600mg)	HDPE bottle 30 tablets	\$169	\$14.1	\$0.469					✓ <sup>1,2</sup>		
TDF + FTC + EFV (300/200/600mg)	HDPE bottle 30 tablets	\$194	\$16.2	\$0.539					✓ <sup>1,2</sup>		
ATV (300mg) + RTV 100mg + TDF /3TC (300/300mg)	Blister Pack of 30 tablets each of ATV + RTV + TDF/3TC	\$395	\$32.9						✓ <sup>4</sup>		

\* Abbott, the originator for the heat-stable formulation of RTV, has an access pricing policy of its own and has not joined CHAI's ceiling price agreement. The company supplies the drug at a reduced price of \$42 per person per year to its Category 1 countries, which includes countries in sub-Saharan Africa and all other Least-Developed Countries. Thus, when the individual components are purchased separately from different suppliers, the TDF+3TC+ATV+RTV regimen is available at less than \$410 per person per year.

## THE CLINTON HEALTH ACCESS INITIATIVE — ANTIRETROVIRAL (ARV) PRICE LIST

PAEDIATRIC PRODUCT		CEILING PRICE (USD)			SUPPLIER			
Name and strength	Packaging	Per Year	Per Pack	Per Unit	Aurobindo	Cipla	Matrix	Strides
3TC (50mg/5ml)*	HDPE bottle 240ml	\$28	\$1.85	\$0.008	✓ <sup>2</sup>			
ABC (20mg/ml)*	HDPE bottle 240ml	\$203	\$13.50	\$0.056	✓ <sup>2</sup>	✓ <sup>1</sup>		
ABC 60mg	HDPE bottle 60 tablets	\$125	\$5.20	\$0.087	✓ <sup>2</sup>		✓ <sup>1,2</sup>	
ABC (60mg) + 3TC (30mg)	HDPE bottle 60 tablets	\$151	\$6.30	\$0.105	✓ <sup>2</sup>		✓ <sup>1</sup>	
AZT (50mg/5ml)*	HDPE bottle 240ml	\$63	\$2.10	\$0.009	✓ <sup>2</sup>			
AZT (100mg)	HDPE bottle 100 capsules	\$34	\$4.75	\$0.048	✓ <sup>2</sup>	✓ <sup>1,2</sup>		
AZT (60mg) + 3TC (30mg)	HDPE bottle 60 tablets	\$78	\$3.25	\$0.054	✓ <sup>2</sup>		✓ <sup>1</sup>	
AZT (60mg) + 3TC (30mg) + NVP (50mg)	HDPE bottle 60 tablets	\$102	\$4.25	\$0.071			✓ <sup>1,2</sup>	
d4T (1mg/ml)*	HDPE bottle 200ml	\$47	\$1.30	\$0.007	✓ <sup>2</sup>			
d4T (15mg)	HDPE bottle 60 capsules	\$16	\$1.35	\$0.023	✓ <sup>2</sup>			
d4T (20mg)	HDPE bottle 60 capsules	\$8	\$1.40	\$0.023	✓ <sup>2</sup>			
d4T (6mg) + 3TC (30mg)	HDPE bottle 60 tablets	\$46	\$1.90	\$0.032		✓ <sup>2</sup>		
d4T (12mg) + 3TC (60mg)	HDPE bottle 60 tablets	\$40	\$3.30	\$0.055		✓ <sup>2</sup>		
d4T (6mg) + 3TC (30mg) + NVP (50mg)	HDPE bottle 60 tablets	\$55	\$2.30	\$0.038		✓ <sup>1,2</sup>		
d4T (12mg) + 3TC (60mg) + NVP (100mg)	HDPE bottle 60 tablets	\$52	\$4.30	\$0.072		✓ <sup>1,2</sup>		
EFV (50mg)	HDPE bottle 30 tablets	\$27	\$2.24	\$0.075	✓ <sup>2</sup>		✓ <sup>2</sup>	
EFV (200mg)	HDPE bottle 90 capsules	\$34	\$8.55	\$0.095	✓ <sup>2</sup>		✓ <sup>2</sup>	
EFV (200mg)	HDPE bottle 90 scored tablets	\$38	\$9.60	\$0.107				✓ <sup>1,2</sup>
LPV/r (100/25mg)	HDPE bottle 120 tablets	\$214	<b>\$17.85</b>	<b>\$0.149</b>	✓ <sup>2</sup>		✓ <sup>1</sup>	
LPV/r (80 +20 mg/ml)*	HDPE bottle 300ml	\$240	<b>\$48.00</b>	<b>\$0.160</b>		✓ <sup>3</sup>		
NVP (50mg/5ml)*	HDPE bottle 240ml	\$59	<b>\$1.95</b>	<b>\$0.008</b>	✓ <sup>2</sup>			

\* Price includes a measuring device such as a syringe, which was not included in the prior ceiling price list.



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# GLOSSARY AND ABBREVIATIONS

**3TC:** lamivudine; nucleoside analogue reverse transcriptase inhibitor.

**ABC:** abacavir; nucleoside analogue reverse transcriptase inhibitor.

**AIDS:** Acquired Immune Deficiency Syndrome.

**API:** active pharmaceutical ingredient.

**ARIPO:** African Regional Intellectual Property Organisation. There are currently seventeen states which are party to the Lusaka Agreement and therefore members of ARIPO. These are: Botswana, Gambia, Ghana, Kenya, Lesotho, Liberia, Malawi, Mozambique, Namibia, Sierra Leone, Somalia, Sudan, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe.

**ARV:** Antiretroviral medicine to treat HIV/AIDS.

**ATV:** atazanavir, protease inhibitor.

**AZT:** zidovudine (also abbreviated to ZDV), nucleoside analogue reverse transcriptase inhibitor.

**BI:** Boehringer Ingelheim.

**BMS:** Bristol-Myers Squibb.

**Category 1:** In this document, 'Category 1' is used to describe those countries that are eligible for the most discounted price offered by a company.

**Category 2:** In this document, 'Category 2' is used to describe those countries that are not eligible for the lowest prices reserved for category 1 countries, but are nevertheless offered a discount by companies. Crucially, this discount is usually considerably smaller than the discount offered to category 1 countries.

**CCRS:** chemokine coreceptor 5.

**CHAI:** Clinton Health Access Initiative. Since 2002, the Clinton Health Access Initiative has assisted countries in implementing large-scale, integrated care, treatment and prevention programmes.

**CHF:** Swiss franc.

**CIF:** 'Cost Insurance and Freight'. A commercial term (incoterm 2000) meaning that the seller delivers once the goods pass the ship's rail in the port of shipment. The seller must pay the costs and freight necessary to bring the goods to the named port of destination BUT the risk of loss or damage to the goods, as well as any additional costs due to events occurring after the time of delivery, are transferred from the seller to the buyer.

**CIP:** 'Carriage and Insurance paid to...'. A commercial term (incoterm 2000) meaning that the seller delivers the goods to the carrier nominated by him, but the seller must in addition pay the cost of carriage necessary to bring the goods to the named destination. This means that the buyer bears all the risks and any additional costs occurring after the goods have been delivered. However, in CIP the seller also has to procure insurance against the buyer's risk of loss of or damage to the goods during carriage. Consequently, the seller contracts for insurance and pays the insurance premium.

**CL:** see compulsory licence.

**Compulsory licence:** A licence to exploit a patented invention granted by the state upon request of a third party.<sup>1</sup>

**Counterfeit drugs:** Drugs which are deliberately and fraudulently mislabelled with respect to identity or source. Counterfeiting can apply to both branded and generic products. Counterfeit products may include products with the correct ingredients or the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging.<sup>1</sup>

**Data exclusivity:** A legal provision that data collected (e.g. the results

of clinical trials) for the purpose of obtaining marketing approval may not be used for a specified period by regulatory authorities to grant approval to a generic product.<sup>1</sup>

**d4T:** stavudine; nucleoside analogue reverse transcriptase inhibitor.

**ddl:** didanosine; nucleoside analogue reverse transcriptase inhibitor.

**Differential pricing:** The practice of setting different prices for different markets, typically higher prices in richer markets and lower prices in poorer markets.<sup>1</sup>

**DDU:** 'Delivered duty unpaid'. A commercial term (incoterm 2000) meaning that the seller delivers the goods to the buyer, not cleared for import, and not unloaded from any arriving means of transport at the named place of destination. The seller has to bear the costs and risks involved in shipping the goods, other than, where applicable, any 'duty' (which includes the responsibility for the risks of the carrying out of the customs formalities, and the payment of formalities, customs duties, taxes and other charges) for import in the country of destination. Such 'duty' has to be borne by the buyer as well as any costs and risks caused by his failure to clear the goods for the import time.

**Divisional patent:** A type of patent application which contains matter from a previously filed application.

**DRV:** darunavir, protease inhibitor.

**EC:** enteric-coated.

**EFV:** efavirenz; non-nucleoside analogue reverse transcriptase inhibitor. Also abbreviated to EFZ.

**EMA:** European Medicines Agency. Formerly European Agency for the Evaluation of Medicinal Products.

**Essential medicines list (EML):** First published by WHO in 1977, it serves to identify a list of medicines, which provide safe and effective treatment for infectious and chronic diseases affecting the vast majority of the world's population. The 17th edition of the adult list and the 3rd edition of the children's list were published in March 2011.

**ETV:** Etravirine, non-nucleoside reverse transcriptase inhibitor.

**EU:** European Union.

**Evergreening:** A term popularly used to describe patenting strategies that are intended to extend the patent term on the same compound.<sup>1</sup>

**Expert review panel:** An independent technical body composed of external technical experts, hosted by the WHO Department of Essential Medicines and Pharmaceutical Policies. Their purpose is to review the potential quality risk of using antiretroviral, anti-tuberculosis and antimalarial products which are not yet WHO prequalified or authorised by a stringent regulatory authority, and to give advice to the Global Fund whether procurement of such products can be authorised.

**EXW:** 'Ex-works'. A commercial term (incoterm 2000) meaning that the seller delivers when he places the goods at the disposal of the buyer at the seller's premises or another named place (i.e. works, factory, warehouse etc.) not cleared for export and not loaded on any collecting vehicle.

**FDC:** fixed-dose combination – multiple drugs combined in a single pill.

**First-line drugs:** The drugs used as a first resort to treat a disease.

**FOB:** 'Free on board'. A commercial (incoterm 2000) term meaning that the seller delivers when the goods pass the ship's rail at the named port of shipment. This means that the buyer has to bear all costs and risks of loss or damage to the goods from that point. The FOB term requires the seller to clear the goods for export.

**FPV:** fosamprenavir; protease inhibitor.

**FTC:** emtricitabine; nucleoside analogue reverse transcriptase inhibitor.

**Generic drug:** According to WHO, a pharmaceutical product usually intended to be interchangeable with the originator product, which is usually manufactured without a licence from the originator company.

**GPRM:** WHO Global Price Reporting Mechanism. A database containing prices paid by UNICEF, the International Dispensary Association (IDA), Management Sciences for Health (MSH)/Deliver, and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

**GSK:** GlaxoSmithKline.

**HDI:** Human Development Index. A summary composite index, compiled by UNDP, that measures a country's average achievements in three basic aspects of human development: longevity (or life expectancy at birth), knowledge (or adult literacy rate and enrolment in education), and a decent standard of living (gross domestic product per capita).

**HIV:** Human Immunodeficiency Virus.

**IDV:** indinavir; protease inhibitor.

**LDCs:** Least-Developed Countries, according to United Nations classification.

**LPV/r:** lopinavir/ritonavir; boosted protease inhibitor.

**MSF:** Médecins Sans Frontières, Doctors Without Borders.

**MVC:** maraviroc; entry inhibitor.

**NFV:** nelfinavir; protease inhibitor.

**NGO:** Non-Governmental Organisation.

**NIH:** National Institutes of Health.

**NNRTI:** Non-Nucleoside Reverse Transcriptase Inhibitor.

**NRTI:** Nucleoside Analogue Reverse Transcriptase Inhibitor.

**NtRTI:** Nucleotide Reverse Transcriptase Inhibitor.

**NVP:** nevirapine; non-nucleoside analogue reverse transcriptase inhibitor.

**OAPI:** Organisation Africaine de la Propriété Intellectuelle, African Intellectual Property Organisation, whose member states are Benin, Burkina Faso, Cameroon, Central

African Republic, Chad, Congo, Côte d'Ivoire, Gabon, Guinea, Guinea-Bissau, Equatorial Guinea, Mali, Mauritania, Niger, Senegal, Togo.

**Patent:** An exclusive right awarded to an inventor to prevent others from making, selling, distributing, importing or using the invention, without licence or authorisation, for a fixed period of time. There are usually three requirements for patentability: novelty (new characteristics which are not 'prior art'); inventive step or non-obviousness (knowledge not obvious to one skilled in the field); and industrial applicability or utility.<sup>1</sup>

**Patent Cooperation Treaty:** An international patent law treaty, concluded in 1970 that provides a unified procedure for filing patent applications to protect inventions in each of its contracting states. A patent application filed under the PCT is called an international application, or PCT application.

**Patent pool:** A patent pool for medicines has the potential to increase access to patented medicines for people living with HIV in the developing world, by creating a structure for patent holders to share their HIV drug patents and receive royalties in return. Drug companies can then access these patents to produce more affordable versions of the patented medicines. Companies are financially rewarded, and patients benefit from access to more affordable medicines. The Medicines Patent Pool was formally established in July 2010.

**PCT:** See Patent Cooperation Treaty.

**PEPFAR:** President's Emergency Plan for AIDS Relief, a United States programme to fight HIV/AIDS in developing countries.

**PI:** Protease Inhibitor.

**PMTCT:** Prevention of Mother-to-Child Transmission.

**ppy:** per patient per year.

**r:** low-dose ritonavir, used as a booster.

**R&D:** research and development.

**RAL:** raltegravir; integrase inhibitor.

**RTV:** ritonavir; protease inhibitor.

**Second-line drugs:** Second-line drugs are used when the first-line drugs are no longer effective.

**Stringent regulatory authority:**

A medicines regulatory authority which 'is (a) a member of the International Conference of Harmonization (ICH); a (b) an ICH observer, being the European Free Trade Association as represented by Swiss Medic, Health Canada and World Health Organization; or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein (as may be updated from time to time).'<sup>2</sup>

**SQV:** saquinavir; protease inhibitor.

**TB:** tuberculosis.

**TDF:** tenofovir disoproxil fumarate; nucleotide reverse transcriptase inhibitor.

**Tentative FDA approval:** Is awarded by the US FDA to a drug product that has met all required quality, safety and efficacy standards, but is not eligible for marketing in the US because of existing patent protection. Tentative approval does make the product eligible for purchase outside of the US under the PEPFAR programme.

**TMC 207:** Rilpivirine, non-nucleoside reverse transcriptase inhibitor.

**TPV:** tipranavir; protease inhibitor.

**TRIPS:** Trade-related Aspects of Intellectual Property Rights.

**UN:** United Nations.

**UNAIDS:** United Nations Joint Cosponsored Programme on HIV/AIDS. Created in 1996, to lead, strengthen and support an expanded response to the HIV/AIDS epidemic. The six original cosponsors are UNICEF, UNDP, UNFPA, UNESCO, WHO and the World Bank. UNDCP joined in April 1999.

**UNDP:** United Nations Development Programme.

**UNITAID:** is an international drug purchase facility that was established in 2006 by Brazil, Chile, France, Norway

and the United Kingdom and now includes 27 countries to provide new sources of funding to fight HIV/AIDS, malaria and tuberculosis.

**US FDA:** United States Food and Drug Administration.

**VL:** voluntary licence.

**WHO:** World Health Organization.

**WHO Prequalification:** A project originally intended to give United Nations procurement agencies, such as Unicef, a choice of products meeting various standards as certified by WHO. With time, other agencies and governments have found this a useful service.<sup>1</sup>

**WTO:** World Trade Organization.

**ZDV:** zidovudine (also abbreviated to AZT); nucleoside analogue reverse transcriptase inhibitor.

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<sup>1</sup>Public Health innovation and intellectual property rights – Report of the Commission on Intellectual Property Rights, Innovation and Public Health, World Health Organization.

<sup>2</sup>[http://www.theglobalfund.org/documents/psm/List\\_of\\_Countries\\_SRA.pdf](http://www.theglobalfund.org/documents/psm/List_of_Countries_SRA.pdf)

## **ACKNOWLEDGEMENTS:**

### **Front and back cover photos:**

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### **Design/artwork/print:**

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